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Mini-Review

Role of Statin in Diabetes

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Abstract

Type 2 diabetes is emerging as another pandemic in India, which requires an aggressive approach in terms of treatment and care. "Diabetes Lipidus" needs on time addressing and initiation of oral hypoglycemic drugs by choosing a patient-centric approach, lipid-lowering agents to prevent the patients from micro and macrovascular complications of diabetes. Primary prevention by statins is very important. Diabetes education and awareness is the key to preventing the emotional, psychological and financial burden of the patient.

Keywords: Type 2 diabetes mellitus, cardiovascular disease, myocardial infarction, total cholesterol, high-density lipoprotein, low-density lipoprotein

Introduction

As per the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study data, there are currently 62.4 million people from diabetes in India.[1] Type 2 diabetes (T2DM) is a progressive chronic lifestyle disorder that hampers the quality of life of the patients due to micro and macrovascular complications causing financial, emotional as well physical stress.(1) Diabetes and dyslipidemia are commonly co-founding complications that lead to atherosclerosis and cardiovascular disease (CVD). The pathological feature of diabetic microangiopathy which occurs in a blood vessel is matrix protein synthesis and thickening of the capillary basement membrane.[1] Along with these changes advanced glycation end products, oxidative stress, low-grade inflammation, and neovascularization of vasa vasorum lead to macrovascular complications.[2] T2DM and cardiovascular complications happen simultaneously at the time of diagnosis, and it has been documented in several studies.[3-6] Nearly all patients, even those under the age of 40 years in India, are at a high risk of CV events and require lipid-lowering therapy in the form of statins to ameliorate the risk.[7] However, CVD remains the leading cause of morbidity and mortality in individuals with T2DM and rates of CVD mortality are two to four times higher in diabetes than in those without diabetes.[8,9] Approximately, >55% of the Indian population is suffering from dyslipidemia. Diabetic dyslipidemia or "diabetes lipidus" is a new evolving terminology. These are two separate risk factors for atherosclerosis. Diabetes and dyslipidemia are two parallel roads that lead to an overt diagnosis of diabetes.[10]

As we are already overburdened with 2nd highest population in the world, these foresee complications can be prevented by appropriate intervention in terms of optimizing weight, drug compliance, lifestyle modification and promoting physical activity. Initiation of appropriate oral hypoglycemic drugs along with timely detection of high-risk cardiac patients, intervention with statins can prevent them from going into disastrous outcome of myocardial infarction. In India, due to unawareness, people often look for a complete cure of diabetes and opt for "wonder medicine" which is often misleading. Medicine non-compliance is the biggest challenge we face in our clinical practice. Lipid-lowering agents are being missed either by clinician or patient's negligence. One of the main reasons for this negligence could be resource-limited setting, cost of statin (as the patient and some health care providers withdraw statin from prescriptions of diabetes patients as they think that statins are extra pills in the treatment of diabetes patients), financial constraints, etc.

Diabetes and Macrovascular Association

Patient with uncontrolled diabetes is at risk of micro and macrovascular complications, particularly CVD. Diabetic patients without previous history of myocardial infarction (MI) have a high risk of MI as nondiabetic patients with previous MI,[11] therefore all diabetic patients should be treated aggressively for the prevention of CVD events. Elevated LDL cholesterol levels should be addressed initially with tight glycemic control which can be achieved with diet, exercise, and antidiabetic agents may substantially improve the lipid profile and reduce the risk of CVD in some patients as per the current American Diabetes Association (ADA) and National Cholesterol Education Program (NCEP) guidelines.[12,13] However, few patients might need intensive lipid-lowering therapy to reduce their cardiovascular risk, most commonly with one of the statins or fibric acid derivatives.[14] The Collaborative Atorvastatin Diabetes Study (CARDS) has shown significant improvement before and after statin treatment.[15] In this randomized study, 2800 diabetic patients without any history of cardiovascular disease were given statin 10 mg versus placebo. At the end of the study, they concluded a relative risk reduction of 37% (p= 0.001).

Collaborative Atorvastatin Diabetes Study: Atorvastatin Significantly Reduces Major Cardiovascular Events in Diabetes Mellitus Patients[15]

Patients were randomized to atorvastatin 10 mg/day (n=1,428) or placebo (n=1,410). Total cholesterol was reduced by 54 mg/dL and LDL by 46 mg/dL in the atorvastatin arm (p<0.0001 each) (**Table 1**). The primary endpoint occurred significantly less frequently in the atorvastatin arm versus placebo (5.8% vs. 9.0%, relative risk reduction [RRR] 37%, p=0.001), as did acute coronary events (3.6% vs. 5.5%, RRR 36%), and stroke (1.5% vs. 2.8%, RRR 48%).

Table 1. The CARDS study showing changes in cholesterol values from baseline to end of study

	Baseline	End of Study
LDL	118.5 mg/dL	82 mg/dL
TG	173 mg/dL	143 mg/dL
HDL	54 mg/dL	49 mg/dL

Pharmacological Therapy in Dyslipidemia

The priority is to bring down LDL levels in diabetic dyslipidemia. Statins are considered as the first drug choice, followed by ezetimibe (a novel cholesterol-lowering drug that acts at the brush border of the small intestine), then fenofibrate or niacin.

The 2013 ACC/AHA guidelines have divided individuals into 4 groups as per atherosclerotic cardiovascular disease (ASCVD) events with a good margin of safety from moderate- or high-intensity statin therapy.[16]

Four statin benefit groups:

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) 190 mg/dL
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL without clinical ASCVD
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age and have LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of 7.5%. This requires a clinician-patient discussion.

If a single agent is inadequate to achieve lipid goals, combinations of the preceding drugs may be used. For elevated triglyceride levels, hyperglycemia must be controlled first by using a patient-centric approach. If triglyceride or high-density lipoprotein levels remain uncontrolled, pharmacologic agents should be considered. Fibrates are slightly more effective than niacin in terms of lowering triglyceride levels, but niacin is the only drug that increases HDL levels appreciably more than fibrates.[17] In this line stream, we have another molecule, saroglitazar which is an insulin sensitizer that acts as a dual PPAR agonist at the subtypes α (alpha) and γ (gamma) of the peroxisome proliferator-activated receptor (PPAR). This is in indicated patients with diabetic dyslipidemia uncontrolled solely on statins.[18]

Statins are a class of drugs widely known as 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors which work by inhibiting the synthesis of cholesterol in the liver by the enzyme HMG-CoA reductase. Several statins are available with various efficacy. Different statins require different dosing to reach the same LDL level such as rosuvastatin, atorvastatin and simvastatin. Statins, except atorvastatin, are usually dosed at night because of higher nocturnal cholesterol synthesis.[19] Some studies have shown the effectiveness of alternate-day dosing of simvastatin.[13]

Statin therapy should be added as adjunctive therapy to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients >40 years irrespective of gender or type of diabetes. Risk doubles with overt cardiovascular disease or family history of CVD. In 2006, a target of <70 mg/dL LDL goal has become a "reasonable goal" in the guidelines for secondary prevention jointly issued by the American Heart Association (AHA) and the American College of Cardiology (ACC).[9]

New Recommendations for Dyslipidemia in Diabetes Mellitus as per the European Society of Cardilogy, 2019[10]

- In patients with T2DM at very high risk (this group includes those with established cardiovascular disease and additional risk factors such as diabetes mellitus, continued cigarette smoking, metabolic syndrome, renal failure and acute coronary syndrome), LDL-C reduction >50% from baseline and LDL-C goal of <1.4mmol/L (<55mg/dL) is recommended.
- In patients with T2DM at high risk, LDL-C reduction of > 50% from baseline and LDL-C goal of <1.8mmol/L (<70mg/dL) is recommended.
- Statins are recommended in type 1 diabetes mellitus (T1DM) patients who are at high or very high risk.

2019 American College of Cardiology and American Heart Association Guidelines on the Primary Prevention of Cardiovascular Disease Statin Recommendations[20]

For Type 1 Diabetes Mellitus Patients (Table 2)

- All people with T1DM and age >40 years (moderate intensity)
- Diabetes >10 years (moderate intensity)
- All T1DM <40 years with documented nephropathy (moderate intensity)
- T1DM <40 years with CVD risk (moderate intensity)
- T1DM >20 years of duration, less or more than 40 years (high intensity)

Table 2. Statin dosing and the AHA classification of intensity[21]

Statin dosage	Low-intensity (LDL-C reduction <30%)	Moderate intensity (LDL-C reduction 30% to <50%)	High intensity (LDL-C reduction >50%)
Atorvastatin	NA	10 to 20 mg	40 to 80 mg
Fluvastatin	20 to 40 mg	40 mg 2×/day; XL 80 mg	NA
Lovastatin	20 mg	40 mg	NA
Pitavastatin	1 mg	2 to 4 mg	NA
Pravastatin	10 to 20 mg	40 to 80 mg	NA
Rosuvastatin	NA	5 to 10 mg	20 to 40 mg
Simvastatin	10 mg	20 to 40 mg	NA

Abbreviations: ACC- American College of Cardiology; AHA- American Heart Association; LDL-C-Low-density lipoprotein cholesterol; NA- Not applicable.

Precautions in Statins Therapy

Very recent guidelines from the American College of Physicians recommend, once lipid-lowering therapy is started, patients should receive at least a moderate dosage of a statin; and for statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in special situation.[12]

A noteworthy number of diabetic patients will require combination therapy. Except for those that have been previously mentioned, most combinations are safe and effective in diabetic patients.[17] Cautiously, the benefits of combination therapy should be weighed against the risks. Statins are associated with a variety of serious side adverse effects, including myalgia and myopathy along with changes in plasma enzymes of hepatic origin.[24] Before prescribing these drugs, a complete medical history should be elicited from the patient to minimize the occurrence of myotoxicity (**Table 3**). A treating physician should be aware of drug-drug interactions between each statin and specific other drugs and take measures to prevent them.[24] Certain drugs should be avoided consuming with other drugs or substances which are known to hamper the absorption of statin.[24] Patients with renal insufficiency should be closely monitored. Moreover, the risk of myotoxicity may be less when combining a statin with niacin versus a fibrate.[17]

Table 3. Dose limits of various statins with respect to various interacting medications[23]

Statin/interactant	Simva	Lova	Atorva	Rosuva	Prava	Fluva	Pitava
Ketoconazole	Avoid	Avoid					
Posaconazole	Avoid	Avoid					
Boceprevir	Avoid	Avoid	No mention				
Simeprevir	Caution	Caution	Caution	Caution	Caution		Caution
Nefazodone	Avoid	Avoid					
Cyclosporine	Avoid	Avoid	Avoid	5 mg/d	20 mg/d	20 mg/d	
Gemfibrozil	Avoid	Avoid	Avoid	10 mg/d	Avoid	Caution	Avoid
Danazol	Avoid	Avoid					
Tipranavir			Avoid				
Telaprevir			Avoid				
HIV protease inhibitor	Avoid	Avoid	20 mg*	10 mg*			
Verapamil diltiazem	10-mg limit						
Clarithromycin			20-mg limit	40-mg limit			
Itraconazole			20-mg limit				
Fosamprenavir ± ritonavir			20-mg limit				
Nelfinavir			40-mg limit				
Fluconazole						20 mg/d	
Amiodarone	20-mg limit						
Amlodipine							
Ranolazine							

Grapefruit juice	Avoid large quantity	Avoid large quantity				
Niacin	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	
Erythromycin						1 mg/d
Rifampin						2 mg/d

Abbreviations: atorva- Atorvastatin; fluva- Fluvastatin; lova- Lovastatin; Pitava- Pitavastatin; prava- Pravastatin; rosuva- Rosuvastatin; simva- Simvastatin

Statin therapy is not recommended in pre-menopausal patients with diabetes considering pregnancy or not using adequate contraception.[10] More awareness needs to be created at the level of primary physician and emphasis should be laid upon drug compliance in form of "Diabetes Education".[22]

Conclusion

A lot has happened in terms of our understanding of diabetic dyslipidemia. The key authorities in guiding dyslipidemia have joined hands to come out with special recommendations to reduce the controversies. The most important fact is that every people with type 2 diabetes mellitus must be initiated with a statin as primary prevention. Although the current LDL goal of less than 100 mg/dL is controversial, recent trials suggest an even more aggressive approach. Monotherapy with a statin may be sufficient for many patients. However, since patients with diabetes often have multiple lipoprotein abnormalities, it is important to use all available treatment options. More awareness needs to spread at the level of primary care physicians and emphasis should be laid upon drug compliance in form of "Diabetes Education". The entire population of clinicians should be updated for this. The bigger challenge is at the level of patients who frequently stop because of inadequate "Diabetes Knowledge". A pill a day; may save our diabetic population from macrovascular accidents. This tiny effort may also save lots of patients' personal as well as national resources.

Declaration of conflicting interests

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