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ROLE OF SAROGLITAZAR IN DIABETES DYSLIPIDEMIA

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ABSTRACT

Diabetes mellitus (DM) is one of the most dreaded metabolic disorders in the world today. It is the leading cause of morbidity and mortality, and plays a cardinal role in quality of life and health economics. DM is associated with a high prevalence of microvascular and macrovascular complications. DM is a very important cardiovascular (CV) risk factor. Cardiovascular disease (CVD) has been implicated as the prime cause of mortality and morbidity in patients with DM. Hence, treatment of DM goes beyond glycemic control, and demands a multidisciplinary approach that comprehensively targets risk factors inherent in CV events. Lipid abnormalities are undoubtedly common in patients with DM, and they contribute to an increased risk of CVD. A high-risk lipid profile, termed atherogenic dyslipidemia of diabetes (ADD), is known to occur in patients with DM. The use of lipid-lowering agents, a quintessential part of the multifactorial risk factor approach, is a crucial intervention to minimize diabetes-related complications. In this article, we discuss the role of peroxisome proliferator activator receptor (PPAR) alpha/gamma (α/γ) agonist, saroglitazar, in the management of ADD. While statins are irrefutably the first line of drugs for dyslipidemia management in patients with residual CV risk while on a statin, PPAR α/γ agonists have been found to be of substantial benefit.

KEYWORDS :- Diabetes dyslipidemia, cardiovascular risk, Lipoproteins, saroglitazar.

INTRODUCTION

Diabetes mellitus is associated with a considerably increased risk of premature atherosclerosis, particularly coronary heart disease (CHD) and peripheral arterial disease.[1,2]Although more recent analyses have suggested a less

marked effect, most authorities consider diabetes to confer at least a twofold excess risk, independently from other conventional risk factors.[3,4] Even in people without diabetes, fasting blood glucose concentration and glycated hemoglobin (HbA1c) are associated with the risk of vascular disease Dyslipidemia is a common feature of diabetes.[5] There is an association between atherosclerotic cardiovascular disease and serum cholesterol and triglyceride levels in both type 1 and type 2 diabetes.[6,7] The risk of CHD is greater at any given level of serum cholesterol in patients with diabetes and its association with hypertriglyceridemia is stronger than in the general population.[8]Importantly, there is strong and convincing evidence that cholesterol lowering therapy significantly reduces CHD in patients both with and without diabetes.[9,10] There also appears to be no threshold below which a further reduction in low-density lipoprotein (LDL) cholesterol might be beneficial.[11]

CAUSES OF LIPOPROTEIN ABNORMALITIES IN DIABETES

Defects in insulin action and hyperglycemia could lead to changes in plasma lipoproteins in patients with diabetes. Alternatively, especially in the case of type 2 diabetes, the obesity/insulinresistant metabolic disarray that is at the root of this form of diabetes could, itself, lead to lipid abnormalities exclusive of hyperglycemia. Type 1 diabetes, previously termed insulin-dependent diabetes mellitus, provides a much clearer understanding of the relationship among diabetes, insulin deficiency, and lipid/ lipoprotein metabolism. In poorly controlled type 1 diabetes and even ketoacidosis, hypertriglyceridemia and reduced HDL commonly occur. [12] Replacement of insulin in these patients may correct these abnormalities, and well controlled diabetics may have increased HDL and lower than average triglyceride levels. The lipoprotein abnormalities commonly present in type 2 diabetes, previously termed noninsulin-dependent diabetes mellitus, include hypertriglyceridemia and reduced plasma HDL cholesterol. In addition, low density lipoprotein (LDL) are converted to smaller, perhaps more atherogenic, lipoproteins termed small dense LDL.[13] In contrast to type 1 diabetes, this phenotype is not usually fully corrected with glycemic control. Moreover, this dyslipidemia often is found in prediabetics, patients with insulin resistance but normal indexes of plasma glucose.[14] Therefore, abnormalities in insulin action and not hyperglycemia per se are associated with this lipid abnormality. In support of this hypothesis, some thiazoladinediones improve insulin actions on peripheral tissues and lead to a greater improvement in lipid profiles than seen with other glucose-reducing agents Several factors are likely to be responsible for diabetic dyslipidemia: insulin effects on liver apoprotein production, regulation of lipoprotein lipase (LpL), actions of cholesteryl ester transfer protein (CETP), and peripheral actions of insulin on adipose and muscle.[15]

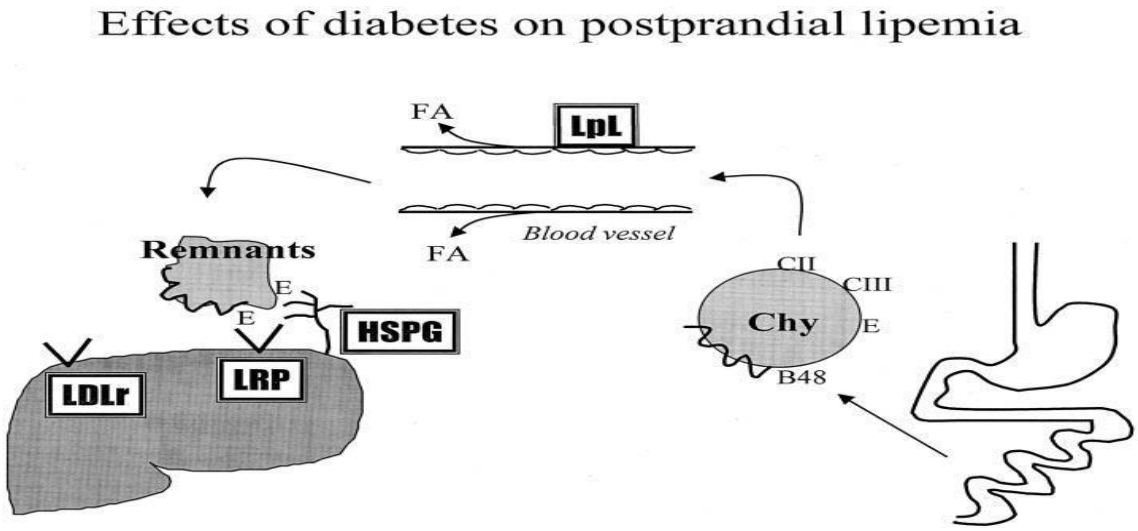


FIG. 1

FIG. 1. Effects of diabetes on postprandial lipemia. A defect in removal of lipids from the bloodstream after a meal is common in patients with diabetes. Chylomicron metabolism requires that these lipoproteins obtain apoCII after they enter the bloodstream from the thoracic duct. Triglyceride within the particles can then be hydrolyzed by LpL, which is found on the wall of capillaries. LpL activity is regulated by insulin, and its actions are decreased in diabetes. Triglyceride-depleted remnant lipoproteins are primarily degraded in the liver. This requires them to be trapped by liver heparan sulfate proteoglycans (HSPG) and then internalized by lipoprotein receptors, LDL receptor and LRP. Because remnants contain a truncated form of apoB, apoB48, that does not interact with these receptors, this uptake is mediated by apoE.

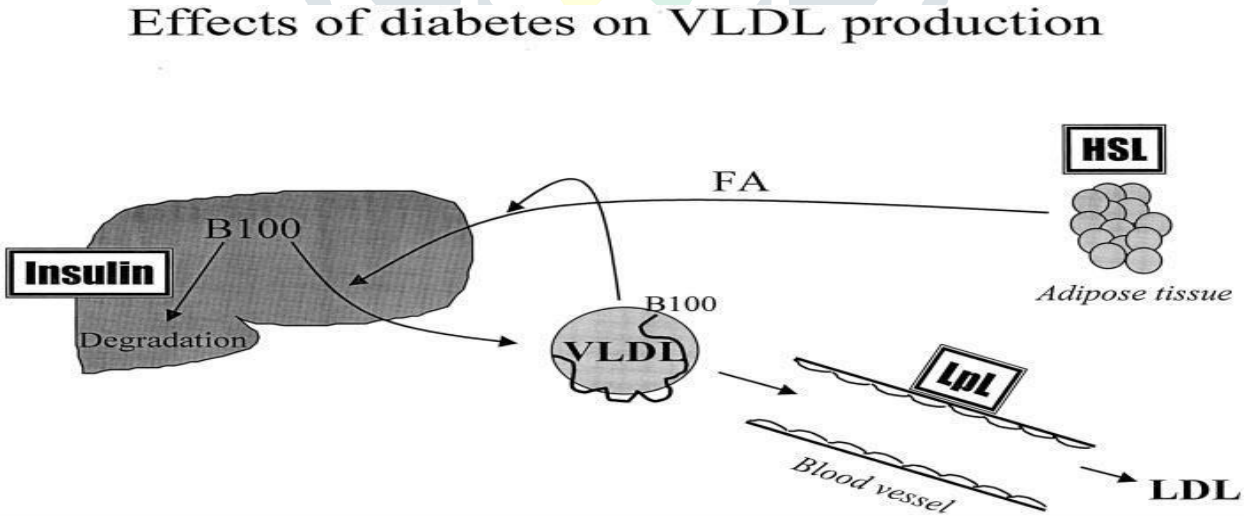


FIG. 2

FIG. 2. Effects of diabetes on VLDL production. Poorly controlled type 1 diabetes and type 2 diabetes are associated with increased plasma levels of VLDL. Two factors may increase VLDL production in the liver: the return of more fatty acids due to increased actions of hormonesensitive lipase (HSL) in adipose tissue and insulin

actions directly on apoB synthesis. Both of these processes will prevent the degradation of newly synthesized apoB and lead to increased lipoprotein production. VLDL, like chylomicrons, requires LpL to begin its plasma catabolism, leading to the production of LDL or the return of partially degraded lipoprotein to the liver.

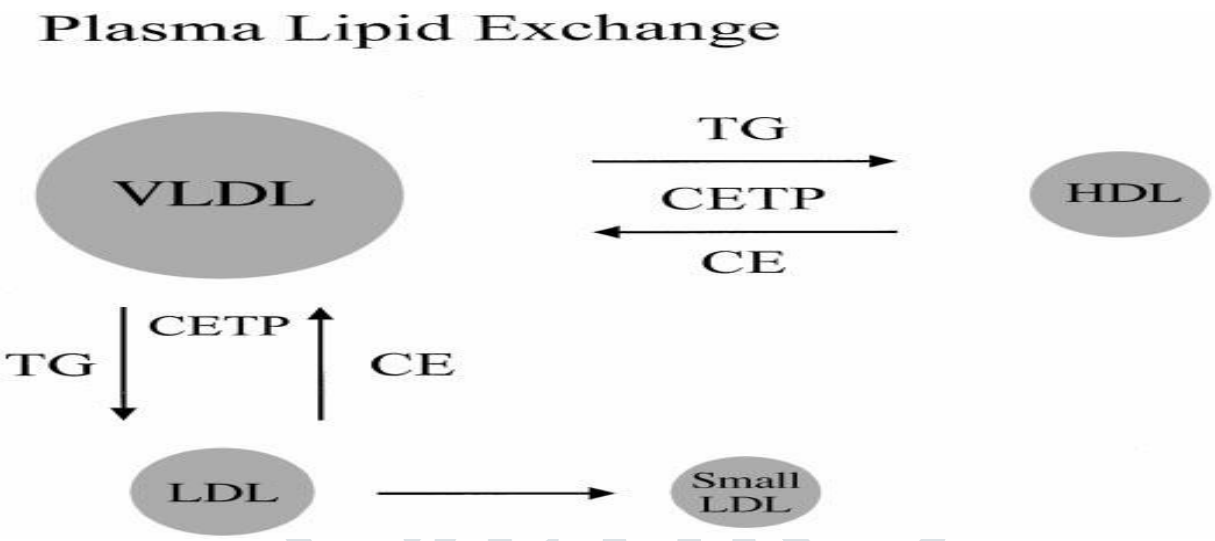


FIG. 3

FIG. 3. Plasma lipid exchange. In the presence of increased concentrations of VLDL in the circulation, CETP will exchange VLDL triglyceride for cholesteryl ester in the core of LDL and HDL. This triglyceride can then be converted to free fatty acids by the actions of plasma lipases, primarily hepatic lipase. The net effect is a decrease in size and an increase in density of both LDL and HDL.

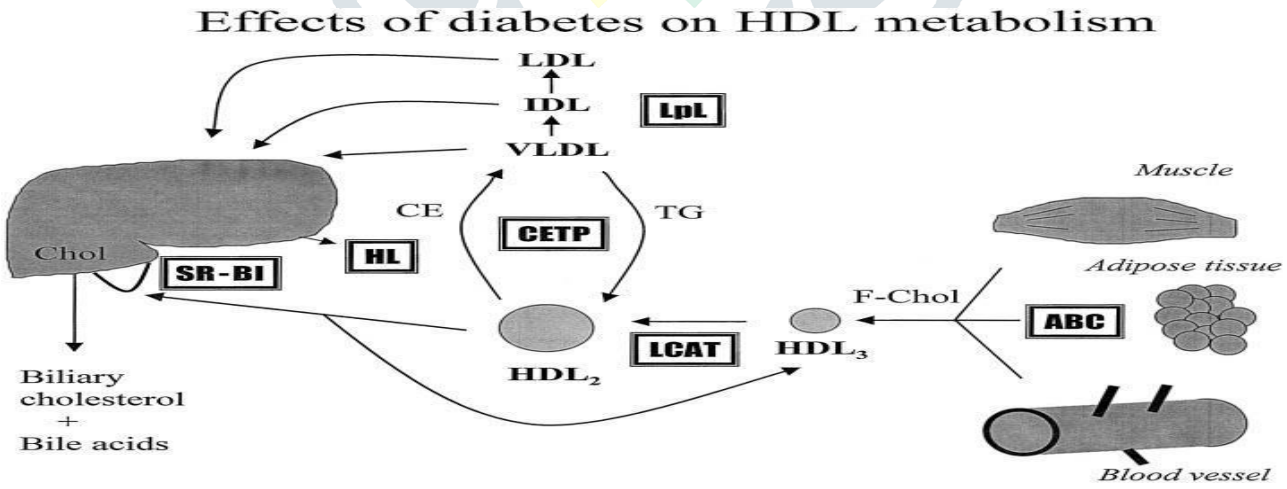


FIG. 4

FIG. 4. Effects of diabetes on HDL metabolism. HDL production requires the addition of lipid to small nascent particles. This lipid arrives via hydrolysis of VLDL and chylomicrons with transfer of surface lipids [phospholipid (PL) and free cholesterol (FC)] via the actions of phospholipid transfer protein (PLTP). A second pathway is via

efflux of cellular free cholesterol (FC), a process that involves the newly described ABC1 transporter and esterification of this cholesterol by the enzyme lecithin cholesterol acyl transferase (LCAT). HDL catabolism may occur through several steps. Hepatic lipase and scavenger receptor-BI are found in the liver and in steroidproducing cells. HDL lipid can be obtained by these tissues without degradation of entireHDLmolecules. In contrast, the kidney degrades HDL protein (apoAI) without lipid, perhaps by filtering

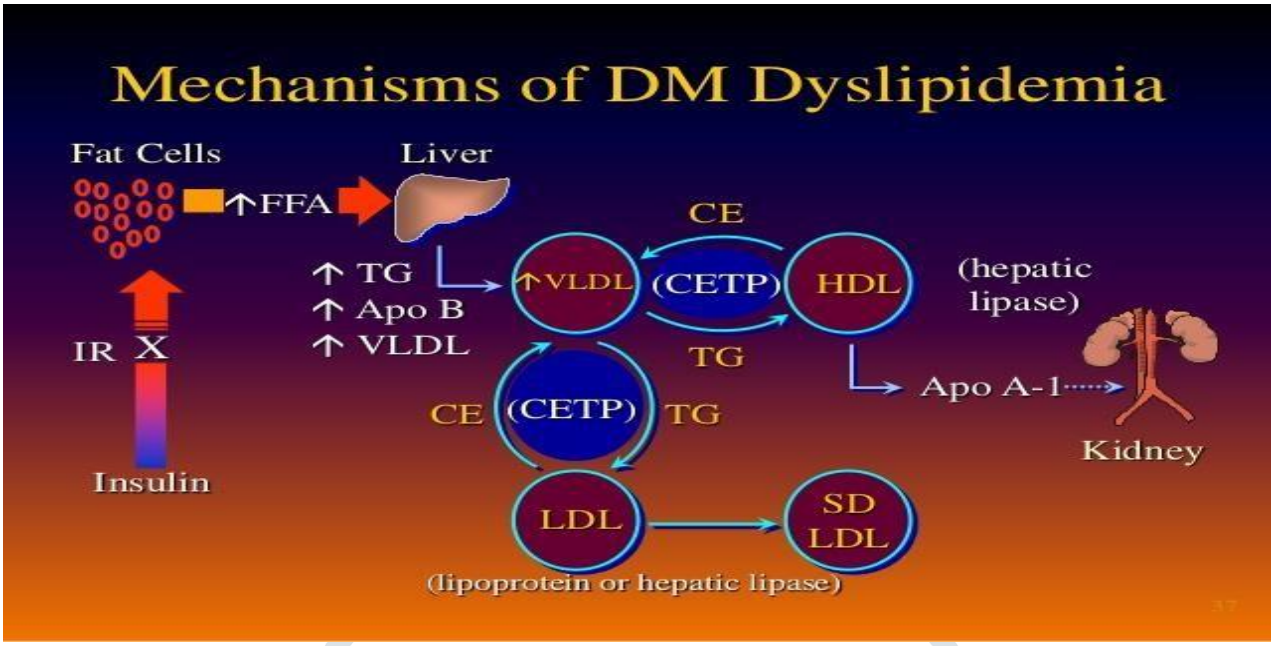
RISK OF CVD IN DIABETES DYSLIPIDEMIA

Cardiovascular disease is more prevalent in type 1 and type 2 diabetes and continues to be the leading cause of death among adults with diabetes. Diabetes coexists as a more severe risk factor with other associating risk factors, in particular with dyslipidemia. It increases cardiovascular risks due to increased levels of triglycerides, low levels of high-density lipoprotein cholesterol, and postprandial lipidemia. Dyslipidemia is mostly observed in patients with type 2 diabetes or metabolic syndrome Among all different types of cardiovascular diseases, atherosclerosis is the main cause of death in the world through causing ischemic heart disease (IHD). This is also associated with endothelial dysfunction, monocyte accumulation, endothelial apoptosis, and thrombus formation which affect cardiovascular functions. Atherosclerosis is partially related to altered serum lipid level, and cholesterol deposition arterial wall that is one of the most important risk factors for coronary artery disease (CAD). In atherosclerosis, the LDL is an important biomarker while high-density lipoproteins are associated with atherosclerotic kidney disease.[16]

LDL-cholesterol has been the primary predictor of CVD. Multiple studies have shown a strong relationship between LDL and CVD. In diabetes, LDL concentration may or may not be increased, but there is an increase in the concentration of small dense LDL particles which are considered more atherogenic than large LDL particles.[17]

MECHANISM OF HYPERTRIGLYCERIDEMIA IN DIABETES

Hypertriglyceridemia is the most common serum lipid abnormality in diabetic populations. Serum TG levels are not simply elevated along with the degree of hyperglycemia, but hyperinsulinemia compensated by insulin resistance is closely correlated with TG levels.[18]TG consists of three molecules of fatty acids, the availability of circulating fatty acids (free fatty acids (FFA)) plays a crucial role in TG production in the liver and partly in the intestineproposed that three distinct syndromes of hypertriglyceridemia occur as a result of abnormalities of glucose metabolism. In patients with impaired glucose tolerance, the basic defect is postulated to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia increased VLDL-TG secretion. Patients with type 2 diabetes have relative insulin deficiency, and the elevated FFA levels increase hepatic VLDL-TG secretion. In absolute insulin-deficient patients with type 1 diabetes, however, elevated FFA levels do not stimulate hepatic VLDL-TG secretion because the livers cannot respond to the increased FFA flux under severe insulin deficiency. The hypertriglyceridemia in patients with type 1 diabetes is primarily due to defect in the removal of VLDL-TG.[19,20]



BENEFITS OF LOWERING TG LEVELS IN T2DM PATIENTS

Many recent studies have shown that lowering of TG levels by PPAR α agonist agents in T2DM patients with ADD can reduce CV events. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9,795 T2DM patients were randomized to fenofibrate or placebo. The follow-up was for 5 years. Serum TG levels were significantly reduced by fenofibrate (by 22%). Fenofibrate reduced CVD events by 27% in the subgroup of ADD patients (baseline: TG .200 mg/dL and HDL-C ,40 mg/dL [21]In the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the use of fenofibrate (in addition to simvastatin) was examined in 5,518 T2DM patients who were at high risk for CVD. The mean follow-up was 4.7 years.Fenofibrate reduced TG levels significantly (by 26%). In the subgroup analysis of patients with ADD (baseline: TG .204 mg/dL and HDL-C ,34 mg/dL), the primary endpoint (the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes) was significantly reduced by fenofibrate (by 31%, P,0.03).20 European Society of Cardiology guidelines for dyslipidemia recommend use of drugs to lower TG in subjects with TG .200 mg/dL who cannot lower them by lifestyle measures, and if the subject is at high total CV risk. As we have discussed, DM patients are at high CV risk.[22]

CURRENT OPTIONS FOR MANAGEMENT OF DIABETES DYSLIPIDEMIA Lipid-lowering agents
Statins

Statin therapy is recommended as the initial pharmacological treatment for lowering LDL-C levels in patients with type 2 diabetes who either have overt CVD or are over 40 years old and have increased CVD risk [23,24] however, even with adequate LDL-C lowering via statin therapy, CVD risk remains high in many patients [25]The beneficial effects of statin treatment are thought to be mediated predominantly via lowering of LDL-C levels, although effects on HDL-C and other lipoproteins may also play a role Statin treatment lowers non-HDL-C more than apoB [26] and reaching the apoB target usually requires more intensive therapy than that required to achieve the non-HDL-C goal

[27,28] Common adverse events associated with statin use include gastrointestinal upset and muscle aches, although dose-related hepatoxicity and myotoxicity are the most clinically significant adverse events [29] Caution is recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min). Studies have shown that high-dose statin therapy is effective in achieving LDL-C goals and associated with favorable effects on lipoprotein subfractions in patients with type 2 diabetes, which may translate into clinical benefits in terms of anti-atherogenic potential and a subsequent reduction in the risk of adverse cardiovascular outcomes.[30,31]

Other lipid-lowering therapies

Niacin has been used to treat dyslipidemia in patients with type 2 diabetes for over half a century.[32] Although niacin is the most effective agent for raising HDL-C levels, high doses can worsen hyperglycemia. Additional adverse events associated with niacin include flushing, itching, nausea, gastrointestinal upset, hypotension, and tachycardia. [33,34] It has been suggested that combination lipid-lowering therapy (eg, a statin with a fibrate or niacin) may be necessary for patients with diabetic dyslipidemia to achieve optimal lipid levels; however, to date, such strategies have not been adequately evaluated for their long-term effect on CVD risk reduction or safety compared with lipid-lowering monotherapy.[35,36] Furthermore, the risk of myopathy is thought to be greater when niacin is used with a statin.[37] Niacin plus laropiprant - a prostaglandin D_2 receptor antagonist and antiflushing agent - has been used successfully to improve the lipid profile with reduced niacin-associated flushing in patients with type 2 diabetes.[38] In 2 large randomized studies in patients with primary hypercholesterolemia or mixed dyslipidemia, the combination of niacin, laropiprant, and simvastatin significantly improved lipid parameters with a similar tolerability profile versus niacin/laropiprant alone, but with an increase in flushing and other niacin-related adverse effects versus statin alone.[39,40]

Ezetimibe, a selective cholesterol absorption inhibitor, is an effective lipid-lowering agent when used as monotherapy and is useful in patients who are unable to tolerate statin therapy.[41] Ezetimibe can also be used in combination with statin therapy for greater lipid-lowering efficacy. Ezetimibe plus atorvastatin, for example, can provide LDL-C lowering equivalent to that achieved with high-dose atorvastatin, but with better tolerability in some patients, and may be a useful adjunctive therapy in patients with type 2 diabetes who have demonstrated an inadequate response to statin treatment.[42]

Fibrates are useful for lowering TG and non-HDL-C levels and increasing HDL-C, yet results from trials in patients with type 2 diabetes have been controversial.[43] In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study in 9795 patients with type 2 diabetes, fenofibrate did not significantly affect the primary endpoint, coronary event rate, relative to placebo (11% reduction).[44] Nevertheless, FIELD did show that combination therapy with a statin and fenofibrate is safe. Recent results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study provided further insight into whether the combination of a statin and a

fibrate is safe and provides CVD benefits beyond statin therapy alone. In this study in 5518 patients with type 2 diabetes, there was no difference between combination therapy with a statin and fibrate compared with statin therapy alone with respect to the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes)[45] Common adverse events associated with fibrates include gastrointestinal disturbance, rash, headache, pancreatitis, myalgia, and myotoxicity (in rare instances - and possibly more likely with gemfibrozil than with fenofibrate.Adjuvant fibrate therapy is not recommended in patients with severe renal dysfunction, severe hepatic dysfunction, and preexisting gall bladder disease.[46]

ROLE OF DUAL PPAR A/Γ AGONISTS IN ADD

Dual PPAR α/γ agonists are newer agents to control all different pathogenetic factors in ADD simultaneously. Their PPAR α agonist action results in increased lipoprotein lipase activity (causing catabolism of TG in VLDL and chylomicrons), reduced secretion of VLDL, inhibition of Apo CIII expression, and increased production of apolipoproteins Apo AI and Apo AII. PPAR
γ agonist actions increase insulin sensitivity in peripheral tissues, increasing glucose uptake, and reduce blood glucose levels.[47]

SAROGLITAZAR: THE FIRST AND ONLY APPROVED DUAL PPAR A/Γ AGONIST

PHARMACOLOGY OF SAROGLITAZAR

Saroglitazar is a dual PPAR α/γ agonist drug approved in India by Drug Controller General of India for the treatment of diabetic dyslipidemia and hypertriglyceridemia with T2DM not controlled by statin therapy. It is the first drug in this novel group of dual PPAR α/γ agonists (glitazars) to be approved and clinically used, anywhere in the world. The recommended dose of saroglitazar is 4 mg per day.

Pharmacodynamics

PPAR α activation by saroglitazar increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of TG. This, in turn, increases diversion of FA from peripheral tissues (eg, skeletal muscle and fat tissue) to the liver, thereby decreasing both FA synthesis and delivery of TG to peripheral tissues. Saroglitazar also causes increased lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase (LPL) and reducing production of Apo C-III, an inhibitor of LPL activity. Saroglitazar was also found to reduce plasma LDL-C. PPAR activation by saroglitazar also induces an increase in the synthesis of apolipoproteins A-I and A-II, and HDL-C.

Although saroglitazar is predominantly a PPAR α agonist, it also causes activation of PPAR γ and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization.

Saroglitazar increases the expression of numerous PPAR γresponsive genes involved in carbohydrate and lipid metabolism, including adiponectin, adipocyte fatty acid-binding protein, LPL, fatty acid transport protein, and fatty acid translocase (CD36). By increasing the expression of these genes, saroglitazar decreases the postprandial rise of plasma FFA, improves postabsorptive, insulin-mediated suppression of hepatic glucose output, reduces the metabolic burden on liver and muscle, and promotes glucose utilization. Robust antidiabetic and insulin-sensitizing effects of saroglitazar were observed in preclinical models, in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. As discussed, saroglitazar is predominantly a PPAR α agonist, with modest PPAR γ agonist actions. This is in contrast to previously developed dual PPAR α/γ agonists, like muraglitazar, aleglitazar, and tesaglitazar, which had either predominantly PPAR γ agonistic activity or equivocal agonistic activity on both PPAR α and PPAR γ receptors.[48]

Pharmacokinetics

In its initial clinical trials, peak plasma levels of saroglitazar occurred at approximately 1 hour post-dosing in healthy volunteers. Its absorption is not affected by food. After a single oral dose of 4 mg saroglitazar in healthy volunteers, maximum serum concentration (C_{max}) of 337.1±91.0 ng/mL (mean ± standard deviation) was observed. It is extensively protein-bound (around 96%) in human plasma. The mean plasma half-life of saroglitazar following a single dose of 4 mg saroglitazar is 2.9±0.9 hours. Multiple-dose studies in humans have not shown any accumulation of saroglitazar on repeat dosing once daily for 10 days.[24]In vitro studies using pooled human liver microsomes showed that saroglitazar is metabolically stable. Saroglitazar was found to be metabolized into three minor oxidative metabolites. The exposure of the most abundant oxidative metabolite was found to be less than 10% of the exposure of saroglitazar. Saroglitazar is excreted primarily through the hepatobiliary route.[49]

Conclusion

ADD is a complex metabolic abnormality seen in most DM patients. Its presence increases CV risk in DM, which is itself considered equivalent to CVD. Traditional drugs like fibrate and niacin can control lipid parameters (hypertriglyceridemia and low HDL-C) in ADD, but do not provide any glycemic benefits; niacin, rather, increases blood glucose levels. Saroglitazar is a novel drug, with unique mechanism of action, which has established its efficacy and safety in diabetic dyslipidemia in clinical trials. It not only corrects lipid abnormalities, but also helps to achieve glycemic targets in T2DM. Further studies should be carried out to evaluate saroglitazar's exact role in management of ADD. Use of saroglitazar will help clinicians to better manage metabolic abnormalities in T2DM patients.

REFERENCES

1. Durrington PN. Hyperlipidaemia: diagnosis and management. London: Hodder Arnold; 2007:33:267-3.

2. Laing SP, Swerdlow AJ, Slater SD, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia. 2003;46:760–5.

3. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–22.

4. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364:829–41.

5. Chapman MJ, Ginsberg HN, Amarenco P, et al. Triglyceride-rich lipoproteins and highdensity lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32:1345–61.

6. West KM, Ahuja MM, Bennett PH, et al. The role of circulating glucose and triglyceride concentrations and their interactions with other ‘‘risk factors’’ as determinants of arterial disease in nine diabetic population samples from the WHO multinational study. Diabetes Care.

1983;6:361–9.

7. Howard BV, Robbins DC, Sievers ML, et al. LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: the Strong Heart Study. Arterioscler Thromb Vasc Biol. 2000;20:830–5.

8. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial.
Diabetes Care. 1993;16:434–44.

9. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364:685–96.

10. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.

11. Cholesterol Treatment Trialists Collaborators, Kearney PM, et al. Efficacy of cholesterollowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a metaanalysis. Lancet. 2008;371:117–25.

12. Ginsberg HN. 1996 Diabetic dyslipidemia: basic mechanisms underlying the common hypertriglyceridemia and low HDL cholesterol levels. Diabetes. 45(Suppl 3):S27–S30.

13. Krauss RM. 1994 Heterogeneity of plasma low-density lipoproteins and atherosclerosis risk. Curr Opin Lipidol. 5:339 –349.

14. Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP. 2000 Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation.
101:975–980.

15. Ginsberg H, Plutzky J, Sobel BE. 1999 A review of metabolic and cardiovascular effects of oral antidiabetic agents: beyond glucose-level lowering. J Cardiovasc Risk. 6:337–346.

16. Rye K.-A. Biomarkers associated with high-density lipoproteins in atherosclerotic kidney disease. Clinical and Experimental Nephrology. **2014;**18**(2):247–250**

17. Jaiswal M., Schinske A., Pop-Busui R. Lipids and lipid management in diabetes. Best Practice and Research: Clinical Endocrinology and Metabolism. **2014;**28**(3):325–338.**

18. Reaven GM: Compensatory hyperinsulinemia and the development of an atherogenic lipoprotein profile: the price paid to maintain glucose homeostasis in insulinresistant individuals. Endocrinol Metab Clin North Am. 2005; 34: 49-62

19. Lewis GF, Carpentier A, Adeli K, Giacca A: Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev. 2002; 23: 201-229

20. Xiao C, Dash S, Morgantini C, Lewis GF: New and emerging regulators of intestinal lipoprotein secretion. Atherosclerosis. 2014; 233: 608-615

21. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study.
Diabetes Care. 2009;32(3):493–498.

22. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, et al, Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–1564.

23. Goff DC, Gerstein HC, Ginsberg HN, Cushman WC, Margolis KL, Byington RP, Buse JB, Genuth S, Probstfield JL, Simons-Morton DG: Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007-99.

24. Standards of medical care in diabetes-2009. Diabetes Care. 2009, 32 (Suppl 1): S13-S61. 10.2337/dc09-S013

25. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL:
Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. 2008, 31: 811-822.

26. Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, Walldius G: Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. Lancet. 2003, 361: 777-780.

27. Stein EA, Sniderman A, Laskarzewski P: Assessment of reaching goal in patients with combined hyperlipidemia: low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, or apolipoprotein B. Am J Cardiol. 2005, 96: 36K-43K. discussion 34K-35K, 10.1016/j.amjcard.2005.08.006

28. Ballantyne CM, Bertolami M, Hernandez Garcia HR, Nul D, Stein EA, Theroux P, Weiss R, Cain VA, Raichlen JS: Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. Am Heart J. 2006-151.

29. Moon YS, Kashyap ML: Pharmacologic treatment of type 2 diabetic dyslipidemia.
Pharmacotherapy. 2004, 24: 1692-1713.

30. High-dose atorvastatin therapy achieves 25% reduction in CV events in TNT substudy of diabetic patients. Cardiovasc J S Afr. 2006, 17: 206-207.

31. Lawrence JM, Reid J, Taylor GJ, Stirling C, Reckless JP: The effect of high dose atorvastatin therapy on lipids and lipoprotein subfractions in overweight patients with type 2 diabetes.
Atherosclerosis. 2004, 174: 141-149. 10.1016/j.atherosclerosis.2004.01.016

32. Nesto RW: Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs. 2005, 5: 379-387.

33. Moon YS, Kashyap ML: Pharmacologic treatment of type 2 diabetic dyslipidemia.
Pharmacotherapy. 2004, 24: 1692-1713.

34. Nesto RW: Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs. 2005, 5: 379-387.

35. Goff DC, Gerstein HC, Ginsberg HN, Cushman WC, Margolis KL, Byington RP, Buse JB, Genuth S, Probstfield JL, Simons-Morton DG: Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control
Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007, 99: 41-20

36. Standards of medical care in diabetes-2009. Diabetes Care. 2009, 32 (Suppl 1): S13-S61.

37. Nesto RW: Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2
diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs. 2005, 5: 379-387.

38. Lauring B, Dishy V, Luo WL, Laterza O, Patterson J, Cote J, Chao A, Larson P, Gutierrez M,
Wagner JA, Lai E: Laropiprant in combination with extended-release niacin does not alter urine 11-dehydrothromboxane B2, a marker of in vivo platelet function, in healthy, hypercholesterolemic, and diabetic subjects. J Clin Pharmacol. 2009, 49: 1426-1435.

39. Shah S, Ceska R, Gil-Extremera B, Paolini JF, Giezek H, Vandormael K, Mao A, McCrary Sisk C, Maccubbin D: Efficacy and safety of extended-release niacin/laropiprant plus statin vs.
doubling the dose of statin in patients with primary hypercholesterolaemia or mixed dyslipidaemia. Int J Clin Pract. 2010, 64: 727-738.

40. Gleim G, Liu N, Thompson-Bell S: Lipid-altering efficacy and safety profile of coadministered extended release niacin/laropiprant and simvastatin in patients with dyslipidemia [abstract 683]. Circulation. 2007, 116: 127-10.1161/CIRCULATIONAHA.107.187674.

41. Nesto RW: Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs. 2005, 5: 379-387.

42. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP: Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003, 107: 2409-2415.

43. Colhoun H: After FIELD: should fibrates be used to prevent cardiovascular disease in diabetes?. Lancet. 2005, 366: 1829-1831.

44. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005, 366: 1849-1861.

45. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP: Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010, 362: 1563-1574.

46. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH: Effects of fibrates on metabolism of statins in human hepatocytes. Drug Metab Dispos. 2002, 30: 1280-1287.

47. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes. 2005;54(8):2460–2470.

48. Lipaglyn (Saroglitazar) [prescribing information]. Ahmedabad, India: Cadila Healthcare; 2013.

49. Jani RH, Kansagra K, Jain MR, Patel H. Pharmacokinetics, safety, and tolerability of saroglitazar (ZYH1), a predominantly PPARα agonist with moderate PPARγ agonist activity in healthy human subjects. Clin Drug Investig. 2013;33(11):809–816.