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Review Article

Atherogenic Dyslipidemia andits Management in Diabetes

Jimimol Thomas*, K. Krishnakumar, L. Panayappan, K. Jayapraksah*
Department of pharmacy practice, St James College of Pharmaceutical Sciences, Chalakudy, Kerala
St James Hospital Trust Pharmaceutical Research Centre, Chalakudy, Kerala

***Corresponding author**
Dr. K. Jayaprakash
Email: stjamespharmacyproject@gmail.com

Abstract: Atherogenic dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. In patients treated with a statin to LDL-cholesterol goals, the addition of ezetimibe, fenofibrate, niacin, or n-3 fatty acid ethyl esters may be required to correct the persistent atherogenic dyslipidemia.
Keywords: Atherogenic dyslipidemia, Type 2 diabetes, Lipids, Lipoproteins, pharmacotherapy.

INTRODUCTION

In 1990, Austin and colleagues first explained Atherogenic Dyslipidemia (AD) as a clinical condition [1] characterized by elevated levels of serum triglyceride (TG) levels and small- dense low-density lipoprotein (sdLDL) particles with low levels of high-density lipoprotein cholesterol (HDL-C), highlighting its atherogenic lipoprotein phenotype[2]. With a focus on type 2 diabetes patients, we review in this article recent clinical trials employing therapeutic agents for the treatment of atherogenic dyslipidemia.

Atherogenic Dyslipidemia

Atherogenic dyslipidemia is one of the metabolic abnormalities that define the metabolic syndrome, the cluster of cardiovascular risk factors frequently associated with intra-abdominal (or visceral) obesity. Diabetic dyslipidemia involves a cluster of lipid and lipoprotein abnormalities. Elevated plasma concentrations of triglycerides and reduced high density lipoprotein cholesterol (HDL-Cholesterol), in both the fasting and postprandial states, are the core lipoprotein abnormalities[3]. Insulin resistance believed to contribute to this atherogenic dyslipidemia by increasing the hepatic secretion of VLDL and other apolipoprotein (apoB)-containing lipoprotein particles, as a result of increased free fatty acid flux to the liver[4,5]. This may also be the result of a diminished suppressive effect of insulin on apoB secretion, either at the level of the regulation of apoB degradation, or inhibition of microsomal TG transfer protein activity[6]. Through the action of cholesterol ester transfer protein, TGs are transferred from VLDL to HDL, creating TG rich HDL particles, which are hydrolyzed by hepatic lipase and rapidly cleared from plasma[7]. A similar cholesterol ester protein-mediated transfer of TGs from VLDL to LDL contributes to the formation of small dense LDL particles[8].

Guidelines for the management of Atherogenic dyslipidemia

Several guidelines provide evidence-based recommendations for addressing diabetic dyslipidemia [9, 10-13]. Two recent reports more specifically on elevated triglycerides and low HDL cholesterol [14].

Table-1: summarizes the recommended treatment targets for diabetic dyslipidemia.

		NCEP ATPIII	ADA	NVDPA	European guidelines
LDL-cholesterol(mmol/l)	Very high risk High risk	< 1.8 < 2.6	< 1.8 < 2.6	< 2.0 < 2.0	< 1.8 < 2.5
Triglycerides(mmol/l)			< 1.7	< 2.0	< 1.7
HDL-cholesterol(mmol/l)	Male Female		> 1.0 > 1.3	≥1.0 ≥ 1.0	>1.0 >1.2
Non HDL cholesterol(mmol/l)	Very high risk High risk	< 2.6 < 3.4	< 2.6 < 3.4	< 2.5 < 2.5	<2.6 <3.3
Apo B (g/l)	Very high risk High risk		< 0.8 < 0.9		<0.8 <1.0

Legend : NCEP ATP III – Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); ADA-American Diabetes Association; NVDPA-National Vascular Disease Prevention Alliance of Australia. In type 2 diabetes, LDL- cholesterol lowering remains the primary focus of therapeutic interventions. Type 2 diabetes patients with overt CVD or high cardiovascular risk should have statin therapy and therapeutic lifestyle changes (TLCs) initiated regardless of baseline lipid levels. In lower risk patients, statin therapy should be initiated if LDL cholesterol levels remain above 2.6mmol/l following TLC efforts or in those with multiple CVD risk factors. These recommendations are supported by evidence of CVD reduction in diabetic patients in large outcome-based clinical trials[15]. If LDL cholesterol reduction is inadequate with a maximum tolerated statin dose, then adding a second therapeutic agent (ezetimibe, fibrate or niacin) may be required. For patients with elevated triglycerides (>2.3mmol/l), the use of non-HDL cholesterol as a secondary treatment target is recommended. ApoB, a measure of LDL particle number is also a recommended treatment target in patients at cardiometabolic risk.

Therapeutic Management

Lipid lowering drugs: 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. 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[16]. Statin-treated patients with low LDL-Cholesterol (<1.8mmol/l) and low triglyceride (<1.7mmol/l) levels had the lowest coronary heart disease (CHD) event rate in the PROVE IT –TIMI 22 trial.Evidence suggests that statins may mediate triglyceride lowering in type 2 diabetes by increasing the catabolism of TRL-triglyceride and TRL's VLDL1-ApoB, VLDL2-ApoB, and IDL-ApoB[17]. The more potent statin, rosuvastatin has been shown to further mediate triglyceride lowering by reducing the production rate and secretion of VLDL1-ApoB[18]. However, this effect has not consistently been shown with statin therapy, indicating that limiting de novo cholesterol synthesis is insufficient for reducing the effects of insulin resistance on hepatic VLDL production. Hence targeting the hepatic production of triglycerides by additional measures such as lifestyle or other pharmacotherapy is required to optimize the management of dyslipidemia in type 2 diabetes.

Fibric acid derivatives: Recent meta-analysis suggested that fibrates may be particularly useful in improving dyslipidemia and preventing CVD in people with mild to moderate chronic kidney disease, including diabetes[19]. The lipid-regulating effects of fibrates, mediated via the peroxisome proliferator-activated alpha (PPAR-α) receptor, predominantly promote fatty acid catabolism and reverse cholesterol transport, resulting in triglyceride lowering and increased HDL-Cholesterol and LDL particle size[20]. Fibrates also increase HDL-Cholesterol by upto 50% and 20%, and enhance the formation of large, less dense LDL-particles Clinical trials also confirm the benefits of fibrates in type 2 diabetes[21-24].

Ezetimibe: It is 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. Eztetimibe 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.

Nicotinic Acid (niacin):At therapeutic doses, niacin exerts a global improvement in lipid and lipoprotein metabolism, and remains the most efficacious therapy available for increasing HDL cholesterol. Niacin has been shown to decrease plasma triglycerides and LDL-cholesterol by up to 35% and 15% respectively, and increase HDL-cholesterol by up to30% in a dose dependent manner.It was suggested in the Coronary Drug Project (CDP) that niacin monotherapy may decrease cardiovascular events and mortality with post-trial follow up demonstrating that the benefits were independent of hyperglycemia, metabolic syndrome,and diabetes.This is important as it has been suggested that niacin impairs glucose/insulin homeostasis.Niacin significantly improves diabetic dyslipidemia, and may deterious effects on glycemic control can be offset by adjusting anti-diabetic therapy.

N-3 fatty acid ethyl esters: Supplementation with n-3 fatty acid ethyl esters (eicosapentaenoic acid (EPA) and docosahexaenoic acid(DHA)), dose dependently lowers plasma triglycerides, particularly in patients with hypertriglyceridemia[25]. Doses of 3-4g daily of EPA and DHA are required. Therefore, commercially available concentrates of n-3 fatty acid ethyl esters, such as omacor, are required for lowering plasma triglycerides. These are FDA approved, as an adjunct to diet, to mitigate the risk of pancreatitis in patients with plasma triglycerides>5.5mmol/l.

CONCLUSION

Atherogenic dyslipidemia is a part of complex cluster of abnormalities called the metabolic syndrome which has a direct correlation with CVD events.

Dyslipidemia is a common risk factor and a strong predictor of CVD in type 2 diabetes. Therapeutic interventions, including lifestyle changes and lipid regulating agents, correct diabetic dyslipidemia via several mechanisms. Recent evidence suggests that residual diabetic dyslipidemia and cardiovascular risk in statin-treated patients with type 2 diabetes may be targeted with fenofibrate.

REFERENCES

1. National Cholesterol Education Program (NCEP); Expert Panel on Detection, Evaluation, Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation, 2002 :106:3143-3421.
2. Genest J, Jr McNamara JR, Ordovas JM, Jenner JL, Silberman SR, Anderson KM, Wilson PW, Salem DN, Schaefer EJ; Lipoprotein cholesterol, apolipoprotein A-I and B and lipoprotein (a) abnormalities in men with premature coronary artery disease. J Am CollCardiol, 1992:19:792-802.
3. Taskinen R; Diabetic dyslipidemia: from basic research to clinical practice. Diabetologia, 2003;46(6):733-749.
4. Krauss RM, Siri PW; Dyslipidemia in type 2 diabetes. Med Clin N Am, 2004; 88:897-909.
5. Laws A, Hoen HM, Selby JV, Saad MF, Haffner SM, Howard BV; Differences in Insulin Suppression of Free Fatty Acid Levels by Gender and Glucose Tolerance Status Relation to Plasma Triglyceride and Apolipoprotein B Concentrations. Arteriosclerosis, thrombosis, and vascular biology, 1997; 17(1):64-71.
6. Malmstrom R, Packard CJ, Caslake M, Bedford D, Stewart P, Yki-Jarvinen H, Shephered J, Taskinen MR; Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM, Diabetologia, 1997;40:454-462.
7. Hopkins GJ, Barter PJ; Role of triglyceride-rich lipoproteins and hepatic lipase in determining the particle size and composition of high density lipoproteins, J Lipid Res, 1986;27:1265-1277.
8. Berneis KK, Krauss RM;Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res, 2002;43:1363-1379.
9. Brunzell J Davidson MM, Furberg CM, Goldberg RM, Howard BP, Stein JM, Witztum JM; 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(4):811.
10. American Diabetes Association; Standards of Medical Care in Diabetes-2013. Diabetes care , 2013; 36:S11-S66.
11. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ; Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Collcardiol, 2004; 44(3): 720-732.
12. National Vascular Disease prevention Alliance; Guidelines for the management of absolute cardiovascular risk. 2012.
13. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S et.al; ESC Guidelines for the management of dyslipidemias. Eur Heart J, 2011; 32(14):1769-1818
14. Miller MM, Stone NJ, Ballantyne CM, Bittner VM, Criqui MH, Ginsberg HN et.al; Triglycerides and cardiovascular disease: A Scientific Statement From the American Heart Association. Circulation, 2011; 123(20):2292-2333.
15. Collins R, Armitage J, Parish S, Sleigh P, Peto R; MRC/BHF Heart protection study of Cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet, 2003; 361(9374):2005-2016.
16. Krishnaswami V; Review articles of Treatment of dyslipidemia in patients with type 2 diabetes; Lipids in health and diseases, 2010, 9:144.
17. Hamilton SJ, Watts GF; Atherogenic dyslipidemia and combination pharmacotherapy in diabetes: recent clinical trials. The review of diabetic studies: RDS, 2012; 10(2-3):191-203.
18. Guyton JR, Bays HE; Safety considerations with niacin therapy. Am J Cardiol, 2007; 99(6A):22C-31C.
19. Jun M, Zhu B, Tonelli M, Jardine MJ, Patel A, Neal B, Liyanage T, Keech A, Cass A, Perkovic V; Effects of fibrates in kidney disease: a systematic review and meta-analysis, J Am Coll Cardiol, 2012;60(20):2061-2071.
20. Gervois P, Fruchart JC, Staels B; Drug Insight: mechanisms of action and therapeutic applications for agonists for peroxisome proliferator-activated receptors, Nat clinpract Endocrinol Metab, 2007;3(2):145-156.
21. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH; Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. Diabetes Care, 1992;15(7):820-825.
22. Keech A, Simes RJ, Barten P; Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type diabetes mellitus (the FIELD): randomized controlled trial. Lancet, 2005; 366(9500):1849-1861.
23. Scott R, O'Brien R, Fulcher G, Pardy C, d'Emden M, Tse, D, et.al; Effects of fenofibrate treatment on cardiovascular disease risk in 9795 individuals with type 2 diabetes and various components of the metabolic syndrome. Diabetes Care, 2009; 32(3):493-498.

24. Ginsberg H; Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med, 2010; 362(17):1563-1574 .
25. Watts GF, Karpe F; Triglycerides and atherogenic dyslipidemia: extending treatment beyond statins in the high-risk cardiovascular patient. Heart 2011; 97(5):350-356.