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Expert's Opinion

Atherogenic Dyslipidaemia - A Relook at the Pathogenesis and Management Options

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Introduction

Atherogenic dyslipidaemia (AD) is a clinical condition characterized by elevated levels of serum triglyceride (TG) levels and small-dense low-density lipoprotein (sdLDL) particles along with low levels of high-density lipoprotein cholesterol (HDL-C).[1] Elevated levels of large TG rich very-low-density lipoproteins (VLDL) and apolipoprotein B (Apo B) and reduced levels of small high-density lipoproteins also occur. These abnormalities usually occur together in obesity, metabolic syndrome, insulin resistance and type 2 diabetes mellitus and have been given this term because it has emerged as an important risk factor for myocardial infarction and cardiovascular disease. Several candidate genes have been linked to AD. Among them, genes coding for lipoprotein lipase (LPL) and apolipoprotein A1 (APOA1) are important due to their roles in regulating both TG and HDL-C levels.[2] Various studies support the increased prevalence of AD in the Asian Indian populations compared to western populations which may probably be attributed to less physical activity and consumption of a diet rich in carbohydrate content and low in PUFA.[3]

Hypertriglyceridaemia

Insulin resistance causes an increased flux of glucose and free fatty acids (due to increased lipolysis) to the liver. It also causes posttranslational stabilization of Apo B which enhances the assembly and unsuppressed secretion of VLDL. Inflammation and low concentration of adiponectin, both of which are present in metabolic conditions result in increased VLDL production thus contributing to hypertriglyceridaemia. Increased concentration and the prolonged postprandial triglyceride-rich lipoproteins as a result of a complex dysregulation of the endogenous (VLDL-IDL-LDL delipidation cascade) and exogenous (chylomicron and chylomicron remnant) lipid pathways found in conditions associated with atherogenic dyslipidaemia. Increased secretion of VLDL-1 lead to increase in sdLDL production and decrease in HDL.[1,4]

Small Dense Low-Density Lipoprotein

The synthesis of sdLDL from TG-rich VLDL-1 involves two steps: transfer of TG from VLDL1 to LDL by cholesteryl ester transfer protein (CETP) and subsequent conversion of TG rich LDL to sdLDL by hepatic lipase (HL). Small dense LDL particles have been shown to predict the rate of IHD independently of LDL cholesterol, triglycerides, HDL cholesterol, apo B and total cholesterol-HDL cholesterol ratio. Several cross-sectional studies have reported differences in LDL particle size, density and composition between patients with coronary heart disease (CHD) and healthy controls with prospective, nested case-control studies showing that small dense LDL particles are associated with a more than 3-fold increase in the risk of CHD. In the Québec Cardiovascular Study, men with an LDL particle size <25.6 nm had a significant 2.2-fold increase in the 5-year rate of ischemic heart disease (IHD) compared with men having an LDL particle size >25.6 nm.[5,6] Multivariate and subgroup analyses indicated that small dense, lipid-poor LDL particles may be inherently more atherogenic than large LDL particles because:

- They have a greater susceptibility to oxidation and therefore may be more likely to instigate the processes of inflammation in vascular endothelium. The oxidized-LDL interacts with scavenger receptors present on endothelial cells, macrophages and smooth muscle cells causing endothelial dysfunction resulting in a build-up of cholesterol within the blood vessel. Other

effects of oxidized-LDL are inhibition of endothelial nitric-oxide synthase (eNOS) expression, adhesion molecule induction, facilitation of monocyte adhesion and infiltration, smooth muscle cell migration and proliferation, including the release of cytokine and growth factor from endothelial and smooth muscle cells all of which enhance the process of atherosclerosis.[1]

- They bind more tightly to arterial proteoglycans and may penetrate the arterial wall more easily.
- They have relatively lower affinity for the LDL receptor compared to mid-size particles, resulting in decreased cellular uptake and increased time spent circulating in the bloodstream thereby having a prolonged influence on the atherosclerotic process.

High-Density Lipoprotein

Apart from sdLDL, cholesteryl ester transfer protein (CETP) and HL also act on VLDL1 to resulting in the production of small HDL. This small HDL has a high clearance from the circulation leading to a decrease in the plasma level of HDL-C and apolipoprotein A1. Every 1 mg/dL increment in HDL-C has been associated with 2 and 3% decreased risk of CHD in men and women, respectively. The anti-atherogenic activities of HDL-C are attributed to:[7]

- Reverse cholesterol transport which involves the transfer of excess cholesterol from lipid-laden macrophages in peripheral tissues to the hepatocytes via HDL for metabolism or excretion into bile.
- Facilitation of vascular relaxation and inhibition of leukocyte chemotaxis and adhesion.
- Counteraction of LDL oxidation.
- Anti-inflammatory and antithrombotic/profibrinolytic effects.

Treatment

Role of Nutritional Diets and Therapeutic Lifestyle Changes

Dietary carbohydrate is considered as the major determinant of raised TG levels in AD. It has been reported that carbohydrate restriction improves atherogenic lipid states even in the absence of weight loss, unlike low-fat diets which require weight loss for effective improvement in atherogenic dyslipidaemia. Approximately, 3-5% reduction in LDL- C has been seen with the increased the use of viscous fibre from 5 to 10 g/day, 6-15% reduction with 2 g/day plant stanols/sterols and 20-30% reduction with use of low saturated fat and cholesterol intake. Other dietary modifications rich in omega-3 fatty acids like the inclusion of soy protein and nuts potentially reduced the levels of LDL-C due to its excellent antioxidant activities. Increased physical activity is one of the most appropriate strategies for managing atherogenic dyslipidaemia. Jogging for six months, regular exercise for eight months and three weeks of diet and brisk walking were found to have significant lowering of LDL-C and comparative increase in larger buoyant LDL particles. A significant increase in plasma HDL-C by 18% was observed with strict adherence to >12 weeks of exercise training.[1]

Role of Statins

Statins have demonstrated significant benefits in hypercholesterolaemia in patients with atherogenic dyslipidaemia. Comparative studies such as the Comparative study with rosuvastatin in subjects with METabolic Syndrome (COMET), Statin Therapies for Elevated Lipid Levels compared across doses to Rosuvastatin (STELLAR) and Satisfying Optimal LDL-C ATP III goals with Rosuvastatin (SOLAR) have shown rosuvastatin to be significantly more effective than atorvastatin in lowering LDL-C levels in these patients.

Role of Fibrates

Fibrates can lower triglycerides between 50% to 85% as also raise HDL levels between 10% and 25% by upregulation of the HDL proteins-apoAI and lipoprotein lipase. Fenofibrate decreases small dense LDL particles in favour of larger, more buoyant LDL particles. Fibrates decrease plasma levels of Lp(a) and reduce fibrinogen. The pleiotropic effects of fibrates may result in direct anti-atherogenic effects in the artery wall by reducing vascular inflammation and decreasing the recruitment of blood cells to the vessel wall. Fenofibrate inhibits activation of vascular smooth muscle cells (SMCs) and lowers C-reactive protein (CRP) levels. Despite these potentially beneficial effects in modifying the typical dyslipidaemia that characterizes the

atherogenic dyslipidaemia complex, fibrate clinical trials have been generally disappointing with respect to CHD prevention other than in the VA- HIT and HHS which may be attributed to the failure of most of the trials to enrol the population with atherogenic dyslipidaemia. In a meta-regression analysis of the fibrate trials, in subjects with baseline values of TGs >2 mmol/L, major CVD events were inversely associated with the magnitude of TG lowering.[8,9]

Role of Cholesteryl Ester Transfer Protein Inhibitors

The exchange of neutral lipids between HDL and triglyceride-rich lipoproteins (TRL) is cholesteryl ester transfer protein (CETP)-mediated and is one of the two major pathways of transporting cholesterol from tissues back to the liver for the purpose of excretion in bile and faeces (reverse cholesterol transport) the inhibition of which increases HDL-C concentration. However, clinical development of CETP inhibitors has been disappointing.[10]

Role of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors facilitate the uptake of LDL-C by improving the recycling of low-density lipoprotein receptor (LDLR) and have shown favourable effects of LDL-C reduction when added to statins.[11]

Novel Therapies Targeting Enhanced Triglyceride Clearance

Apo C3 which inhibits hepatic lipase activity, enhances VLDL secretion and suppresses TRL remnant clearance and other molecules which cause pharmacological inhibition of enzymes involved in TG biosynthesis, namely, diacylglycerol acyltransferase (DGAT) and monoacylglycerol acyltransferase (MGAT) appears promising.[11]

Conclusion

Atherogenic dyslipidaemia is often found in association with many metabolic disorders. All the components of the condition have been individually and in combination seen to be associated with increased cardiovascular risk. Apart from statins, fibrates also have a role to play in the treatment of atherogenic dyslipidaemia. The role of newer molecules needs further study.

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The authors declare no conflict of interest.

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