

## Lipid Triad: An Important Predictor of Dyslipidemia Related Disorders and its Therapeutic Intervention

Shafeeque Ahmad<sup>1\*</sup>, M Mobarak Hossain<sup>1</sup> and Muhammad Anas<sup>2</sup>

<sup>1</sup>Interdisciplinary Brain Research Centre, Jawahar Lal Nehru Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh 202 002, UP, India

<sup>2</sup>Department of Ilmu Advia, H.A.H. Unani Medical College, 3 Idgah Road, Dewas 455001, MP, India

Cardiovascular disease (CVD) is leading cause of premature death worldwide. 30% of all global deaths in 2005, i.e. 17.5 million people died from this CVD. If proper and quick actions are not taken, an estimated number of 20 million people will die by 2015, including stroke [1]. Lavie et al. [2] stated regarding fiscal burden of CVD and, especially, coronary heart disease (CHD), most medical treatments are directed at the major CHD risk factors. CVD implies to any medical disorders related to heart and blood vessels. There are a number of known causative factors that are directly or indirectly responsible for CVD. The lipid triad refers basically to three lipid abnormalities: increased plasma triglycerides and small dense low density lipoprotein (sd-LDL), and decreased high density lipoprotein cholesterol (HDL-C) concentrations. Since lipid triad is highly atherogenic in nature causing CVD, also called as atherogenic lipoprotein phenotype. The liver secretes lipoproteins called very-low-density lipoproteins (VLDL) rich in triglycerides. As these lipoproteins come into contact with lipoprotein lipase situated on capillary endothelial cell, hydrolyzes the triglycerides leaving VLDL remnant. Many patients with premature CHD having cholesterol levels in the range of 200-240 mg/dl show other risk factors like hypertension, obesity or abnormalities in triglycerides metabolism. But these above anomalies are often seen in reduced concentration of HDL [3]. Low density lipoprotein cholesterol (LDL-C) rich in cholesterol has been extensively studied and known for its bad cholesterol because it is considered as a good marker for cardiovascular disease risk assessment [4] and its level in human body should be below 130 mg/dl. HDL-C ranging between 35-40 mg/dl is considered as good cholesterol as it helps in the removal of cholesterol along with it also shows antioxidant property carrying arylesterase/paraoxonase antioxidant enzyme. High level about 60 mg/dl of HDL-C is believed to be played a good protective role in human health protection as it protects efficiently heart from dangerous attack on it. The various previous studies clearly indicate that high concentration of LDL-C and substantially increased ratio of LDL and HDL are important risk factors which promote atherosclerosis [5]. The study for UK Progression of Diabetes Study showed that LDL-C is the strongest risk factor for coronary heart disease followed by HDL-C in this population [6]. Thus it suggested that 0.1 mM rise in HDL-C would decrease coronary heart disease by 15%. LDL particles are differentiated into large buoyant LDL (lb-LDL) and small dense LDL (sd-LDL). These subfractions are associated with difference in size, density, physico-chemical composition, metabolic behavior and atherogenicity. Different known techniques such as density gradient, ultracentrifugation, polyacrylamide gel electrophoresis, nuclear magnetic resonance, etc. are employed for fractionation of LDL into sd-LDL and lb-LDL subfractions [7-9]. lb-LDL particle shows >25.5 nm while sd-LDL particle shows ≤ 25.5 nm.

Oxidative modifications of lipoproteins are considered to play an important role in the pathogenesis of atherosclerosis [10]. Chemically modified LDL in which the lipid components or apo B have been oxidized are endocytosed by macrophage scavenger receptors. Intracellular cholesterol levels are increased, and macrophages are transformed into foam cells, which participate in the formation of atherosclerotic plaque. Sd-LDL subfraction of LDL is more prone to oxidative damage than lb-LDL particle [11]. As we know that

persons having lipoproteins rich in sd-LDL particles are more prone to myocardial infarction. And sd-LDL lipoprotein particles are associated with up to a three-fold greater risk of myocardial infarction [12]. There are various factors that attribute to sd-LDL particles to possess more atherogenic property than lb-LDL particles. These are enhanced susceptibility to oxidative modification, prolonged half life, and higher penetration ability in arterial wall and lower binding affinity property for the LDL-receptor [13], along with highly reduced content of antioxidant and low level of free cholesterol [14-17]. Apart from these properties, there are another attributes that make sd-LDL to more atherogenic like rich in polyunsaturated fatty acids, especially hydroperoxides [14,18]. Thus, these above features make sd-LDL to highly atherogenic that cause atherosclerotic disease.

The lipid-modifying drugs like statins, inhibitor of HMG-CoA reductase (a key enzyme in lipid metabolism), nicotinic acid (niacin) and fibrates that show profound decrease in the level of LDL-C. Statins are also involved in a modest reduction in triglycerides along with increase in HDL through the modulation of cholesterol ester transfer protein. The same effects are also reported after treatment with nicotinic acid that is profound increase in HDL-C, a modest decrease in the levels of triglycerides and LDL-C. On the other hand, administrations of fibrates also resulted in increased production of HDL and lipoprotein lipase that causes reduction in triglycerides by activating the peroxisome proliferator-activated receptor. The lipid-modifying drugs are also shown to alter LDL subfraction distribution [19]. The both fibrates and nicotinic acid decrease the levels of sd-LDL but in another studies, it is found that net effect of these substances was moderate [20]. On the other hand, statins have been reported that these compounds lower the concentrations of all LDL subfractions but it was also shown that a greater decrease in sd-LDL especially with atorvastatin and simvastatin was found [20]. The above drugs which are comparatively safe and well tolerable but a significant number of problems are still suffered by patients like their high cost, especially in poor or developing countries, side effects such as elevations of some liver-enzyme activities, body pain, loss of memory and brain function, etc. So, to overcome these problems, alternative drugs have to be found out. Today research towards natural products is now focused not only to reduce cholesterol level but also to inhibit LDL as well as its subfraction sd-LDL oxidation. Natural antioxidant enzymes and natural antioxidants such as tocopherol, carotenoid,

**\*Corresponding author:** Shafeeque Ahmad, Interdisciplinary Brain Research Centre, Jawahar Lal Nehru Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh 202 002, UP, India, Tel: +91-766946514; E-mail: [azamshafeeque1@gmail.com](mailto:azamshafeeque1@gmail.com)

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bilirubin, thymoquinone that show free radical scavenging properties and protect cellular damage [12,21]. On the other hand, some natural compounds for example, vitamin A, quercetin, curcumin, retinol, lycopene and thymoquinone may be used in oxidative related disorders, atherosclerosis [12,22,23]. Like statins, thymoquinone modifies lipid levels by suppressing HMG-CoA reductase activity. In addition, some physical exercise and diet control should be in practice. Apart from the above points, there are still many questions that are unsolved, such as random generation of reactive oxygen species/free radicals could not clearly explain rate of atherosclerosis and the level of oxidative modification of LDL and its subfractions, and random atherosclerosis lesion on vessel wall, and which antioxidants/natural products can inhibit these disorders, and what is better choice/required doses of natural compounds for different patients that will be effective for the treatments. These are some points which should be under investigation for the treatment of lipid related disorders.

In conclusion, atherogenic lipoprotein phenotype or lipid triad has been characterized by three lipid components namely increased plasma triglycerides, highly atherogenic sd-LDL particle and decrease in HDL-C levels, that cause CVD/ atherosclerosis/CHD. There are some drugs available like statins, nicotinic acid and fibrates which show strong lipid-modifying drugs possessing safe and well tolerable properties. Although, some patients also show side effect, today, there are another some research areas which should be focused on drugs/natural compounds, and such drugs should be cost effective, well tolerable, and easily available, along with various target points that effectively treat the disorders. Thus, future of treatment with hypolipidemic/lipid-modifying drugs is likely to include intervention to increase HDL-C, decrease sd-LDL as well as triglycerides levels in safe dose, cost effective with good potential.

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