

**CARDIOVASCULAR** diseases (CVD) are the leading cause of morbidity and mortality in the developed world, and coronary heart disease (CHD) the number one killer, in the US. Dietary fats, lipid transport and metabolism in the body, atherosclerosis are linked closely with CVD.

Cholesterol, cholesterol esters, triglycerides and phospholipids in the blood and tissues of the body are insoluble in blood (plasma) and lipoproteins, as carrier molecules are required to facilitate their cellular transport.

Abnormal lipoprotein or lipid metabolism may induce hyperlipidemia and hypertriglyceridemia, which define cardiovascular disease etiology.

HDL, termed the 'atherogenic triad', characteristic of atherogenic dyslipidemia is found in people with diabetes, metabolic syndrome and CHD.

Clinical studies and epidemiological analyses correlate high levels of low-density lipoprotein

show that over-expression of apolipoprotein (apo) A-1, the major HDL lipoprotein, inhibits progression and induces regression of atherosclerosis. Clinical studies revealed that increased HDL-C level is an important modifiable ischemic



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# Affairs Of The Heart

Phytonutrients and nutritional interventions to support cardiovascular health and wellness. By **Muhammed Majeed**, founder & owner, & **Lakshmi Prakash**, VP, innovation & business development, Sabinsa

Dyslipidemias, disorders from lipoprotein metabolism, overproduction or deficiency are manifested as elevated plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations and a decrease in the plasma high-density lipoprotein (HDL) cholesterol concentration.

A condition characterised by small, dense LDL particles, elevated triglycerides and low

cholesterol (LDL-C) with atherosclerosis and CVD. Risk factors include cigarette smoking, hypertension, diabetes and a low level of high-density lipoprotein cholesterol (HDL-C).

Healthy diet and disciplined lifestyle are the cornerstones for CHD prevention with drug therapy regimen in people facing a high short-term risk for heart disease.

Most therapeutics target LDL reduction. However, studies

stroke risk factor in the elderly among different racial or ethnic groups.

Therapeutic guidelines for patients with lipid abnormalities emphasise on LDL as the primary target of cholesterol-lowering therapy, optimal HDL levels, healthy body weight and physical activity. Complete lipoprotein profiling (total, LDL, HDL, triglycerides) help screen and assess CHD risk status.

Metabolic syndrome (insulin resistance) patients are advised intensive therapeutic lifestyle changes. Plant sterols/stanols, as therapeutic dietary options to lower LDL cholesterol levels, are also recommended.

## LIPOPROTEINS, DYSLIPIDIMIAS & CVD RISK

The six major classes of plasma lipoproteins are Chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL) or 'bad

cholesterol', high-density lipoproteins (HDL) or 'good cholesterol', lipoprotein (a) (Lp(a)) or 'deadly cholesterol'.

#### RISK LEVELS FOR HEART DISEASE

Elevated levels of C-reactive protein, LDL-C and myeloperoxidase (MPO) are implicated in cardiovascular disease events. Inflammation of atherosclerotic plaques and the subsequent formation of blood clots on their surface are also considered critical leads to most atherosclerosis induced cardiovascular events. HsCRP (high sensitivity C-reactive protein) tests correlate more closely with already established cardiovascular disease risk factors than LDL tests alone.

#### CURRENT THERAPEUTIC AGENTS

Therapy enables patients to achieve target blood lipid and lipoprotein levels. A therapeutic or nutraceutical agent modulates lipid absorption or affects lipid or lipoprotein metabolism, at

different points in the metabolic pathway. Some therapeutic and dietary lipid lowering agents are discussed.

#### STATINS

Most current therapeutic approaches seek to lower LDL-C through statins, which are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate limiting enzyme that catalyses the conversion of HMG CoA to mevalonate in the liver cells.

Mevalonate is the precursor molecule for cholesterol, Coenzymes Q and squalene (an intermediate in cholesterol synthesis). The decrease in intracellular cholesterol level induces a higher surface expression of LDL receptors which consequently increases the clearance of plasma LDL-C.

IDL and VLDL remnants are removed as well, contributing to lowering triglyceride-rich

lipoprotein levels. Statins remarkably reduce major coronary events and mortality rates in patients with CHD, according to a Scandinavian Simvastatin Survival Study Group.

Unfortunately, the mechanism of action of statins through inhibition of the mevalonate pathway inhibits the biosynthesis of vital biochemical products, including coenzyme Q10 (CoQ10) or ubiquinone (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone), a major participant in electron transfer during oxidative phosphorylation, a potent antioxidant and free radical scavenger as well as a membrane stabiliser that preserves cellular integrity.

As such, supplemental CoQ10 becomes indispensable for patients on long-term statin therapy. The US FDA labelling information recommends liver function testing before and 12 weeks after starting statin therapy.



### OTHER LIPID-LOWERING AGENTS

Bile acid sequestrants/resins and cholesterol absorption inhibitors such as ezetimibe lower LDL-C primarily through increased hepatic LDL receptor activity. Plant stanols/sterols, polyphenols, as well as phytonutrients such as oat bran, psyllium and soy proteins also lower LDL-C.

Lipid lowering fibrates, used in patients with mixed or combined hyperlipidemia and hypertriglyceridemia, decrease plasma triglycerides by decreasing their hepatic synthesis and increasing their catabolism. They decrease the triglyceride-VLDL synthesis by enhancing beta-oxidation of fatty acids in the liver and increase the plasma triglyceride catabolism by inducing lipoprotein lipase gene transcription, and decreasing the apoC-III gene transcription. Fibrates also increase HDL-C by increasing apoA-I and apoA-II gene transcription.

Nicotinic acid (niacin), acipimox, high-dose fish oils and antioxidants also affect lipid metabolism beneficially. Drug combinations (fixed-dose) such as extended-release niacin/lovastatin as well as lipid-altering drugs including anti-obesity agents also favorably affect lipid levels. Niacin may be considered an alternative in statins or fibrates intolerant individuals that improves all components of the atherogenic triad, often present in diabetics.

### HEART OF THE MATTER

Soluble fibers slightly reduce LDL-C levels, while insoluble fibers decrease CVD risk. Dietary fibers demonstrated an inverse association with serum concentration of C-reactive protein (CRP). Adequate levels of magnesium are also critical for cardiovascular health. Dietary

sources of soluble fiber are beta-glucan from oats and/or barley and psyllium seed husk.

Daily dietary intake of soy protein also reduces CHD risk. Dietary plant sterol/stanol esters may reduce the risk of CHD and those low in sodium may reduce the risk of high blood pressure.

Plant sterols/stanols, polyphenols, natural antioxidant herbal extracts such as curcuminoids from turmeric, viscous fiber such as oat bran, saponin-rich seed extracts from fenugreek, and seed proteins such as soy protein lower lipid levels and maintain cardiovascular health.



In a 2002 study, US researchers unraveled the mechanism of action of guggulsterones, from the resin of guggul (*Commiphora mukul*) used traditionally in Ayurveda. A guggulsterone-rich extract affects blood lipid levels due to its antioxidant action on oxidised LDL, improvement of insulin sensitivity reduction in blood glucose levels, reduction in Lp(a) levels and increased fecal excretion of bile acids and cholesterol from the intestine.

Guggulsterones serve as antagonist ligands for the bile acid receptor FXR that regulates cholesterol homeostasis. The most recent considerations in cardiovascular diseases

therapy also include indices of inflammation, C-reactive protein (hsCRP), uric acid and lipoprotein(a) levels, besides elevated cholesterol. Clinically, Gugulipid was shown to benefit the combination of factors.

Policosanol, the natural mixture of higher aliphatic alcohols, found in sugarcane wax, has been clinically proven to maintain normal cholesterol metabolism. Policosanol lowered total cholesterol and LDL-C effectively and increased HDL-C levels, besides inhibiting platelet aggregation and aiding in intermittent claudication. In in vitro studies, policosanol inhibited cholesterol synthesis in the liver, but direct inhibition of the hydroxy-methylglutaryl-coenzyme A reductase (the mechanism of action of statins) was unlikely.

Policosanol effectively lowered platelet aggregation with efficacy comparable to aspirin at a dose level of 20 mg, with a combination of Policosanol and aspirin being more efficacious at dosages of up to 20 mg per day. Successful studies were done mostly with policosanol from Cuban sugarcane. A clinical study done with policosanol obtained from Indian sugarcane also revealed its significant lipid lowering benefits in South Asian subjects.

Turmeric and ginger provide cardiovascular health promoting natural compounds. Curcuminoids, the yellow pigment in turmeric roots benefit cardiovascular health by providing antioxidant (bioprotectant) support, anti-inflammatory support, anti-platelet aggregation support and positively influence lipid metabolism, increasing HDL-C levels while lowering LDL-C levels and triglyceride levels.

Ginger extract also lowers



LDL-C and elevated blood pressure and has anti-platelet aggregation and vasodilatory effects. Its hypotensive action is postulated to occur through a dual inhibitory effect mediated via stimulation of muscarinic receptors and blockade of calcium ion channels.

Nearly two thirds of the saturated fats in coconut oil are Medium Chain Triglycerides (MCTs). A 30-day clinical study revealed beneficial effects of MCT as compared to LCT (olive oil) on body composition, energy expenditure, energy intake and subjective appetite.

Sesamin and sesamol, from sesame seed oil that enhance the oxidative stability of the oil, decrease the concentration of serum total cholesterol and VLDL in laboratory studies. Sesamin inhibits the micellar solubility of cholesterol and liver microsomal HMG CoA reductase activity. Sesamin with vitamin E suppressed age related elevation in blood pressure and showed vasodilatory effects.



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**PERSONALISED NUTRITION**

Studies suggest that lipoprotein particle sizes are heritable, and encourage a healthy aging phenotype, associated with a lower prevalence of hypertension, cardiovascular disease, metabolic syndrome and increased homozygosity for the I405V variant in CETP.

The hypothetical peroxidation of LDL as an initial step in atherosclerosis and the discovery of the body's inherent antioxidant enzyme, paraoxanase, associated with HDL, have fueled widespread research interests.

Citrus flavonoids, naringin and naringenin lower the expression levels of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1), with potential applications in the prevention of atherosclerosis. Similarly, MMP-

8 (matrix-metalloprotein 8) a collagenase enzyme expressed in atherosclerotic plaques is a target for the treatment of CVD. Phytonutrients inhibiting the expression of this enzyme would therefore prevent cardiovascular problems. From this perspective, genomic tools would enable individualised approaches to a healthy heart through lifestyle, nutritional and phytonutrient interventions, in the years to come.

A comprehensive approach to support healthy blood sugar, blood lipid and blood pressure levels that includes a healthy diet, exercise and lifestyle measures, in combination with supplemental nutrients, would be most conducive to cardiovascular health and wellness.



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