Beyond Cholesterol

by Chris D. Meletis, ND and Kimberly Wilkes

In pursuit of disease management, the status quo of the westernized medical model all too often becomes myopic in regards to risk management. One of the best examples of this is cardiovascular disease, which encompasses so much more than cholesterol management. Yet billions of dollars per year of statin drugs are prescribed along with generalized diet and lifestyle recommendations without adequate testing for other risk factors for cardiac health.

The hyper-focus on cholesterol means that not only are people over-treated for lipid problems but also, if their cholesterol levels are normal, they are given a clean bill of health when in reality other cardiovascular concerns may be brewing under the surface. Far too many of Dr. Meletis' patients in his clinical practice in Portland, Oregon, have participated in corporate wellness programs and have been given glowing results. The patients will arrive at the clinic, proudly stating that their cholesterol levels are great. They will present with numbers such as total cholesterol 187, low-density lipoprotein (LDL) 120, high-density lipoprotein (HDL) 57, and fasting glucose 87.

These numbers are definitely a good start, yet further testing reveals a completely different picture in regards to their risk of cardiovascular disease. These same patients who thought they had a clean bill of health actually have raised levels of other cardiovascular risk factors such as small particle pattern LDL as well as less than favorable Lp-PLA2 levels and an imbalance in apolipoprotein B (ApoB) and lipoprotein(a), to name a few.

This article will review these and other often neglected cardiovascular disease risk markers and interventions that proactive functional medicine providers use to enhance their patients' circulatory health.

An Inflammatory Disease

There is a lot of evidence to show inflammation is a major culprit for all the major cardiovascular concerns. In fact, scientists now believe inflammation is actually a cause of cardiovascular disease and not just a consequence.[1] One way scientists know that there is a strong link between inflammation and cardiovascular disease is because levels of two inflammatory markers – C-reactive protein (CRP) and fibrinogen – are elevated in people who suffer from heart disease and stroke. In one study, elevated fibrinogen and high CRP levels independently predicted subclinical atherosclerosis in postmenopausal women with hypertension, whereas established traditional cardiovascular risk factors such as obesity, diabetes, smoking habits, family history of coronary artery disease, and high cholesterol did not have as strong an association with the disease.[1]

Higher levels of CRP are associated with an increased risk of developing ischemic heart disease (IHD).[2] CRP causes inflammation in cells lining the coronary arteries known as endothelial cells.[3] This means CRP may be directly involved in the inflammatory component of atherosclerosis.[3] In another study, patients with the highest levels of C-reactive protein (more than 10 mg per liter) were significantly more likely to die from cardiac causes compared with people whose CRP levels were 2 to 10 mg per liter or less than 2 mg per liter.[4]

High CRP levels also are associated with stroke. Researchers compared the CRP levels in people who had a more severe type of stroke (progressive cerebral infarction) with a less severe type (non-progressive cerebral infarction).[5] In the subjects with the more severe type of stroke, there was a significant rise in CRP three days after the stroke, followed by a decline on day 7 and day 14, and the CRP level was much higher compared with people who had a less severe stroke. In patients on statin drugs, scientists have found that high CRP levels increase the risk of having a stroke in the future.[6]

Statin drugs are known to significantly reduce CRP levels by up to 60% and therefore may have anti-inflammatory actions, but statin drugs may also dramatically reduce levels of coenzyme Q10,[7] a nutrient critical for heart health. In addition, statins damage the mitochondria,[8] the powerhouses of the cells that also are critical to heart health. Consequently, there may be an advantage to relying on natural agents to reduce CRP levels. For example, people who regularly take more than 78 mg vitamin E/day along with vitamin C, carotenoids, selenium, and zinc, have 22% lower high-sensitivity CRP

levels compared to people who don't supplement with vitamin E.[9] A review of 12 studies involving a total of 246 participants given vitamin E and 249 people given a placebo found that two forms of vitamin E, alpha-tocopherol or gamma-tocopherol, were effective at lowering CRP levels.[10]

Like CRP, elevated fibrinogen levels are another indication of inflammation. Fibrinogen plays a critical role in blood clots through its conversion to fibrin, the main component of a clot's structure. Fibrinogen rises every decade of a person's life by an average of 25 points. This elevation in fibrinogen increases the viscosity of the blood, making it "thicker." Clinical studies have demonstrated higher levels of fibrinogen in people with cardiovascular disease and who have an increased risk of blood clots.[11] Evidence from human studies indicates the likelihood of dying from cardiac causes is greater in people with the highest fibrinogen levels (at least 4.0 gram per liter) compared with people who have the lowest levels (less than 3.4 g per liter).[4]

Two of the most effective natural agents used to lower fibrinogen levels, reduce the risk of stroke, and improve the health of the circulatory system are nattokinase and lumbrokinase. Nattokinase is a fermented soy extract derived from the traditional Japanese food natto. Human studies have shown nattokinase can reduce certain cardiovascular risk factors and that an important mechanism of action is the reduction of fibrinogen. In one study, healthy volunteers, people with cardiovascular risk factors, and dialysis patients were given two capsules of nattokinase (2,000 fibrinolytic units per capsule) daily for two months.[12] Plasma levels of fibrinogen as well as two other coagulation factors (factor VII and factor VIII) continuously declined during nattokinase supplementation. Nattokinase did not affect blood levels of lipids.

Nattokinase can also reduce blood pressure, another risk factor for stroke, according to a double-blind, randomized, placebo-controlled study where supplementation with nattokinase was associated with a drop in both systolic and diastolic blood pressure.[13] Although the decline in systolic blood pressure occurred in both genders, it was greater in males taking the nattokinase supplement, whereas in the females ingesting nattokinase, researchers also observed a decline in von Willebrand factor (vWF), which is involved in coagulation.

Like nattokinase, lumbrokinase benefits the heart in part through its ability to reduce fibrinogen levels.[14,15] Due to its clot-destroying activity, lumbrokinase has been used in ischemic encephalopathy, coronary heart disease, diabetes, and deep vein thrombosis.[14] In patients with cerebral infarction (stroke), lumbrokinase inhibits coagulation and reduces fibrinogen by increasing the activity of tissue plasminogen activator (t-PA), a protein that plays a role in the breakdown of blood clots.[16]

Niacin is another natural substance that can lower fibrinogen levels, and studies have also shown it can reduce CRP levels.[17] Niacin should be used with caution in diabetics as it can worsen blood sugar levels.[17]

The Powerhouses of the Cells Protect the Circulatory System

Mitochondria are the cell's batteries, and these powerhouses are responsible for producing ATP, the fuel the body needs for metabolic processes. Needless to say, these tiny organelles are responsible for the proper functioning of many organs in the body and the heart is no exception. Mitochondrial dysfunction may play an important role in the development of atherosclerosis.[18] Mitochondrial DNA (mtDNA) damage can increase inflammation,[18] and inflammation, as noted earlier in this article, is directly linked to cardiovascular disease.

Human and animal studies have found that an increase in the generation of reactive oxygen species (ROS), also known as free radicals, the build up of mtDNA damage, and dysfunction in the mitochondria's respiratory chain are all related to atherosclerosis or cardiomyopathy.[19-21] When researchers gathered aortic samples from people with severe atherosclerosis and compared them to samples from people without this condition, they found that people with atherosclerosis had more mtDNA damage compared to the people without.[22]

In mice, the extent of mtDNA damage matches the severity of atherosclerotic lesions and precedes the development of atherosclerosis.[22] Mitochondrial dysfunction also increased mtDNA damage and advanced the development of atherosclerosis in mice, supporting the belief that ROS generation and mtDNA damage occurs early in the development of atherosclerosis.[22]

Additionally, conditions involved in the development of atherosclerosis such as high cholesterol, high blood sugar, high triglyceride levels, and aging itself all cause mitochondrial dysfunction.[19,23] Researchers have shown that high levels of serum LDL cholesterol and triglycerides in mice cause mitochondrial damage and dysfunction, which leads to the development of atherosclerosis lesions and affects their composition and progression.[23]

Over time, excessive generation of mitochondrial reactive oxygen species destroys the insulin-producing beta-cells of the pancreas, increases oxidation of LDL cholesterol, and harms the endothelial cells lining the blood vessels.[19] Each of these factors encourage the development of atherosclerosis.[19]

Properly functioning mitochondria are also required for the normal growth and function of vascular cells. Dysfunctional mitochondria trigger a process called apoptosis that results in the removal of unhealthy cells.[24] However, apoptosis encourages the rupture of plaques, which in turn enhances the progression of atherosclerotic lesions.[24] Plaque rupture can lead to heart attacks and strokes.[19] Oxidized LDL, a more harmful form of LDL cholesterol that has been attacked by free radicals, triggers apoptosis of cells involved in plaque rupture and atherosclerosis,[25,26] and mitochondria dysfunction is involved in this process.[27] This may explain why the oxidation of LDL is an important step in the development of atherosclerosis.[27]

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Mitochondrial dysfunction is associated with hypertension, another cardiovascular disease risk factor.[19] Declines in mitochondrial energy and calcium overload are involved in the development of hypertension.[19,28] In mice where the mitochondrial antioxidant system is dysfunctional, arterial blood pressure rises with age or when eating a high-salt diet.[29] In humans, mitochondrial mutations lead to hypertension, high cholesterol, and low magnesium levels.[30]

People who have diabetes are at a greater risk of developing coronary artery disease,[31] and people with type 2 diabetes are more likely to experience ischemic events and death after a first heart attack.[32,33] One of the ways in which diabetes may increase the risk of cardiovascular disease is through mitochondrial dysfunction.[34] Research indicates that mitochondrial dysfunction is involved in the vascular damage caused by glucose.[34] Lowering levels of mitochondrial ROS prevents blood-sugar-related damage and the formation of advanced glycation end products (AGE), harmful compounds involved in vascular damage and atherosclerosis.[34]

Given the role that mitochondrial dysfunction plays in diabetes, it is disturbing that conventional treatment for type 2 diabetes includes statin drugs. As noted earlier in this article, statin drugs cause mitochondrial dysfunction.

Due to the mitochondria importance in cardiovascular health, supplements that support mitochondrial function may be beneficial. One of the most well-known mitochondrial-supporting supplements is coenzyme Q10 (CoQ10). People who received 300 mg/day of CoQ10 supplements for 2 weeks before cardiac surgery experienced improved mitochondrial CoQ10 levels in their hearts and enhanced mitochondrial efficiency.[35] During cardiac surgery, arteries are deprived of oxygen as the blood supply is stopped; and when the blood and oxygen supply is reintroduced, it leads to hypoxia-reoxygenation stress, which is damaging to the heart. CoQ10 improves the heart tissue's tolerance to this hypoxia-reoxygenation stress.[35]

Alpha-lipoic acid and acetyl-L-carnitine, two other agents known to enhance mitochondrial function, improved arterial health in a study of people with hypertension.[36] Over eight weeks, the combination of alpha-lipoic acid and acetyl-L-carnitine lowered systolic blood pressure in all 36 subjects. The blood-pressure-lowering effect was the most significant in participants with higher blood pressure and in subjects with the cluster of heart disease risk factors known as the metabolic syndrome.

Antioxidant supplements can help support the mitochondria by controlling levels of ROS and reduce the oxidation of LDL. Green tea, CoQ10, red wine, and red grape seed extract are just some of the supplements and dietary components that can lower oxidized LDL.[37-40]

An Often-Neglected Aspect of Cardiovascular Health

When physicians evaluate cardiac risk factors in their patients, one aspect of cardiovascular health that is often neglected is testing nitric oxide levels. Maintaining optimal levels of nitric oxide is crucial for the health of the cardiovascular system. Lower levels of nitric oxide are associated with many cardiovascular diseases including hypertension, atherosclerosis, stroke, and heart failure.[41] Scientists believe that increased levels of ROS are to blame for decreased nitric oxide absorption.[41]

L-Citrulline and beetroot juice both have a lot of research backing up their ability to raise nitric oxide levels. Heart failure is characterized by increased activity of angiotensin–converting enzyme and reduced peripheral blood flow, both of which reduce the generation of nitric oxide.[42] L-Citrulline has improved dilation of the blood vessels of stable systolic heart failure patients.[42] Studies also have shown that L-citrulline can reduce arterial stiffness in middle-aged men and postmenopausal women[43,44] and that it can reduce postoperative pulmonary hypertension.[45] L-Citrulline is especially effective when combined with the antioxidant glutathione, since glutathione prevents the oxidative damage to nitric oxide caused by exposure to ROS.[46]

Beetroot juice works in a manner similar to L-citrulline in that is raises levels of nitric oxide.[47] In peripheral arterial disease, not enough blood reaches tissues resulting in intermittent claudication pain during walking. In peripheral arterial disease patients, beetroot juice increased nitric oxide levels and improved peripheral tissue oxygenation in areas of hypoxia (low oxygen).[48] It also increased exercise tolerance, and patients given beetroot juice walked for 17% longer compared to people taking a placebo.[48] In addition, studies have shown beetroot juice enhances vascular function in people with high cholesterol[49] and improves muscle power in individuals with systolic heart failure.[50]

A Good Night's Sleep Equals a Healthy Heart

During obstructive sleep apnea, a person stops breathing intermittently throughout the night. Sleep apnea can mirror peripheral ischemia as sleep apnea literally is low oxygen levels due to nighttime desaturation. When asking a patient about how they are sleeping, a doctor recognizes it is just as much about how much oxygen the person is receiving as it is about insomnia.

There is a strong link between sleep apnea and daytime hypertension and it may also be associated with pulmonary hypertension, stroke, coronary artery disease, and cardiac arrhythmias.[51] One study of Hispanics found that sleep apnea increases the risk of peripheral artery disease.[52] People with sleep apnea also have increased carotid and aortic wall thickness and high-risk carotid atherosclerosis plaques.[53]

Proper sleep in a dark room also allows the body to secrete healthy amounts of melatonin, a hormone that acts like an antioxidant. Melatonin is important in maintaining the endothelium, the lining of the blood vessels.[54] An analogy can be made between a healthy blood vessel (the circulatory system) and a non-stick pan. It is not until there is damage to the

non-stick coating that there is an issue with the frying pan and food begins to stick. Yet, it's not the item that is sticking to the pan that caused the problem in the first place. It was the problem with the non-stick coating. The endothelium lining of the blood vessel walls is like that non-stick coating. Therefore, we must address issues that are occurring in the endothelium, otherwise it will do no good to lower cholesterol.

Melatonin is an important ally in keeping the endothelium strong and healthy.[54] To study the effect of melatonin on the endothelial cells lining the blood vessels, researchers evaluated this hormone's effects on intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), CRP, and nitric oxide in patients with three-vessel coronary disease.[54] The study participants were given either 10 mg oral melatonin one hour before sleeping for one month or a placebo. After one month, people taking the melatonin experienced a significant drop in levels of ICAM, VCAM, and CRP while people taking the placebo experienced an increase in VCAM. Nitric oxide levels also increased in the melatonin group, whereas they decreased in the placebo group.

According to the researchers, "The results of this study suggested that melatonin may have beneficial effects on endothelial oxidative stress even in patients with severe and advanced atherosclerosis."

Genetic Risk Factors

Folate is critical for cardiovascular health. Yet, due to a genetic mutation in the gene for methylenetetrahydrofolate reductase (MTHFR), many people lack the ability to convert the folic acid found in supplements and fortified foods into the biologically active form of folate known as L-5-Methyltetrahydrofolate (L-5-MTHF). Functional medicine providers often look for this genetic risk factor, specifically the MTHFR 1298 mutation and C677T mutation. When these mutations are not adequately compensated for, it's common for homocysteine levels to also be elevated.[55] Homocysteine is an amino acid linked to cardiovascular disease.

Often one of the first clues that a person has a MTHF mutation is that their mean corpuscular volume (MCV) is starting to creep above 90. The average red blood cell lives 90 to 120 days and can serve as the proverbial coal miner's canary in regards to vitamin B12 and folate deficiency. It is important that anyone with these MTHF mutations supplement with L-5-MTHF rather than folic acid.

Cholesterol Isn't the Only Lipid To Be Worried About

Besides LDL cholesterol, there are several other lipid risk factors for coronary heart disease and stroke, yet these risk factors are usually ignored in conventional medicine settings. One of these lipid risk factors is lipoprotein-associated phospholipase A2 (Lp-PLA_2), an enzyme that serves as a marker for vascular inflammation and rupture-prone plaque.[56] Most heart attacks and strokes are caused by ruptured plaque rather than blocked blood vessels. Higher Lp-PLA_2 activity is associated with a greater risk for fatal and nonfatal coronary heart disease events.[57] Because Lp-PLA_2 is vascular specific, testing for it can be more beneficial than testing for CRP,[58] which is a marker for systemic inflammation and can be elevated for other reasons besides heart disease.

Another lipid-related cardiovascular risk factor is small dense low-density lipoprotein particles, which are especially prone to triggering atherosclerosis and are much more harmful than larger particle LDL. This is why only testing total and LDL cholesterol levels does not present a complete picture of a person's coronary health. One study found that eating a Mediterranean diet supplemented with nuts increased the LDL particle size.[59]

Finally, it's also important to monitor levels of lipoprotein(a) and apolipoprotein B (ApoB), components of lipids involved in atherosclerosis and cardiovascular disease. Niacin is one supplement known to lower lipoprotein(a) levels[60] while omega-3 fatty acids have lowered ApoB.[61]

Other Cardiovascular-Supporting Supplements

In addition to the dietary supplements already discussed in this article, other nutrients show promise in enhancing circulatory health. Berberine is a botanical that has anti-inflammatory, antioxidant, and heart-protective properties.[62] In patients with congestive heart failure, 1.2 to 2 grams/day of berberine decreased ventricular premature complexes and reduced mortality.[63] Berberine also improves insulin resistance, which is another way in which it improves cardiovascular health.[64]

Another important addition to a cardiovascular health regimen is vitamin D. Low levels of vitamin D are linked to peripheral artery disease[65] and an increased risk of heart attacks.[66] Vitamin D combined with gamma-tocopherol, vitamin C, and tetrahydrobiopterin (BH4) was effective in blocking atherogenesis and formation of plaques.[67] Vitamin E reduces the risk of venous thromboembolism[68] while B vitamin deficiency may increase the risk of venous thrombosis.[69]

Conclusion

Cholesterol is only one piece of the cardiovascular disease puzzle. Other, possibly even more important, risk factors for heart disease and stroke include fibrinogen, CRP, mitochondrial dysfunction, nitric oxide levels, sleep apnea, the MTHFR genetic mutation, Lp-PLA_2, small dense low-density lipoprotein particles, lipoprotein(a), and ApoB. The most effective regimens for supporting cardiovascular health address all of these risk factors.

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