Dynamic Chiropractic

Cholesterol Update: Oxidized asnd Nonoxidized LDL Cholesterol

Cholesterol is *not* inherently a harmful thing-it actually serves many essential purposes in our bodies. For instance, it acts as the main precursor for testosterone and estrogen. However, it is well known that alterations in cholesterol levels and ratios, i.e, increased total cholesterol, low high-density lipoprotein (HDL) cholesterol, and elevated low-density lipoprotein (LDL) cholesterol are proven risk factors for heart disease. It must be understood, however, that current thought implicates LDL - otherwise known as the "bad" cholesterol - as being especially "bad" when it becomes oxidized. Many drugs and some natural supplements, with results that vary considerably, are used in an effort to lower LDL levels. It is, it seems, always beneficial to lower LDL. What is less commonly known, however, is that LDL must be protected against damage from free radicals-a process that creates *oxidized* LDL.

It is this oxidized, or damaged, form of LDL that research has identified as an important factor in initiating atherosclerosis. Oxidized LDL cholesterol causes a number of deleterious events, including impairment of endothelial cell function in artery walls, inhibition of nitric oxide production by blood vessel cells, enhancement of the release of inflammatory cytokines (chemical messengers that contribute to inflammation and movement of white blood cells to sites of injury), and increased expression of adhesion molecules (proteins that increase the ability of white blood cells to stick to and traverse artery walls).[1] All of these events can be tied to promotion of vascular injury and dysfunction. Clearly, oxidized LDL cholesterol must be targeted if atherosclerosis is to be avoided.

Diabetics at Increased Riskfor Oxidative Stress

Significant segments of the population have been found to encounter increased oxidative stress on a regular, ongoing basis. This warrants mention because increased oxidative stress would lead to higher levels of oxidized LDL. One of the best-studied groups is the diabetic population, where increased oxidative stress is a typical finding. This is not, however, irreversible - studies have shown that the increased oxidative damage to LDL cholesterol found in diabetics can be significantly improved via antioxidant supplementation. In one study, 20 diabetics with elevated LDL oxidation measures were placed on placebo for eight weeks, followed by 12 weeks of beta carotene (24 mg), vitamin C (1,000 mg), and vitamin E (800 IU of d-alpha tocopherol). This combination of antioxidants was found to significantly reduce LDL oxidation.[2] This study is an example of intelligent supplementation, i.e., increased oxidative stress found in a given population was treated with a science-based combination of antioxidants, which led to significant lowering of oxidative stress measures and probable avoidance of future risk of free-radical-associated disease. It's simple, safe, and effective.

Oxidized LDL as Gene Signaling Agent

Oxidized LDL, it turns out, does more than just increase one's risk for clogged arteries - it can act as a signal to your genes. It is now known that oxidized LDL has the ability to increase overall oxidative stress, which in turn activates the gene transcription entity known as nuclear factor-

kappa B (NF-*Kappa* B or NF-$_{K}$B). Other entities, such as free radicals; viruses; lipopolysaccharide from intestinal bacteria (endotoxin); and inflammatory cytokines, such as tumor necrosis, factor *alpha* can also activate NF-$_{K}$B. When oxidized LDL activates this or any of the other substances just mentioned, a large number of genes is signaled.[3] The genes then release their messages, which can include increased production of inflammatory cytokines, adhesion molecules, and nitric oxide (this increase in nitric oxide is seen in joints where it is known to promote inflammation). In general, activation of NF-$_{K}$ B leads to promotion of inflammation and further oxidative stress.

It is essential, therefore, that efforts are made to make sure that LDL does not become damaged by free radicals. This can be effectively accomplished by regularly consuming antioxidants. The two antioxidants that are essential in this process are vitamins C and E. The body cannot make either of these vitamins and both have been shown to work together as a team in helping to decrease oxidative stress. Moreover, they have been shown to decrease oxidative damage to LDL. Doses of 500-1,000 mg of vitamin C, 400-800 IU of vitamin E (preferably the natural form of vitamin E identified as d-alpha tocopherol), plus 10,000-25,000 IU of beta carotene per day should do the trick and help avoid future disease related to oxidized LDL cholesterol.

Non-Oxidized LDL Cholesterol and Loss of Endothelial Cell Function

Although oxidized, or "damaged" LDL cholesterol undoubtedly plays an important role in the genesis of arterial disease, evidence shows that even if LDL is prevented from oxidizing, it might still be a dangerous entity.

Researchers have demonstrated that elevated LDL, whether it is oxidized or not, can alter the endothelial cell's ability to release nitric oxide.[4] This has many beneficial effects on the health of the cardiovascular system, including its essential role in maintaining the ability of arteries to properly dilate when they are supposed to. Studies on nitric oxide and atherosclerosis have shown that:[5]

- the typical appearance of atherosclerotic blood vessels - i.e., structural changes - are preceded by a loss of nitric oxide production;
- experimental inhibition of endothelial nitric oxide synthase (eNOS), the enzyme that produces nitric oxide in blood vessels, leads to progression and worsening of the atherosclerotic plaque; and
- loss of nitric oxide release are seen in homocysteinemia, diabetes, and smoking, leading some researchers to consider low nitric oxide output as a possible common denominator for the development of cardiovascular disease.

The mechanism behind non-oxidized LDL cholesterol's ability to decrease nitric oxide formation relates to an increase in the production inside blood vessel cells of a substance known as caveolin. Caveolin binds to and inhibits the function of eNOS. Again, this is the *only* enzyme that can produce nitric oxide within blood vessels. The LDL cholesterol mediated caveolin-induced loss of eNOS function is thought to be an important early cause of blood vessel endothelial cell malfunction-a predisposing factor related to the development of atherosclerosis.[6]

Addressing Elevated LDL Cholesterol

Many health practitioners believe that as long as LDL cholesterol is protected from oxidation via the use of antioxidants, the risk of developing heart disease will be significantly diminished. Although this may be true to a certain extent, elevated non-oxidized LDL (or elevations of LDL that have been protected from oxidation by using antioxidants) still poses a risk for developing heart

disease through its negative effects on nitric oxide production. Therefore, elevated LDL cholesterol should be addressed from a number of perspectives:

- Attempts should be made to lower LDL cholesterol. Many natural substances have this ability, including red yeast rice; niacin (especially the trademarked Niaspan, a safer "drug" form of niacin with less negative side effects than niacin); artichoke extract; garlic; guggulsterones; soy isoflavones; fiber; and pantethine. However, the brand Cholestin, made by Pharmanex, is my current favorite cholesterol-lowering agent. I have seen total cholesterol drop 60 points or better, with no adverse liver function tests (LFTs), in patients who were previously resistant to treatment with any of the statin medications (such as Lipitor, Mevacor, etc.). In addition, one of the main benefits of statin-like drugs might be their ability to lower C-reactive protein (CRP), one of the most important predictive factors for heart disease that we can measure in blood. Research from Harvard Medical School has shown that pravastatin can lower this blood protein - a fact that points to other beneficial, nonlipid lowering effects of statins.[7]Since red yeast rice is really just a safe source of mixed statins, Cholestin may be shown to have positive effects on CRP as well.

- Antioxidants such as vitamins C, E and beta carotene should be taken to protect against the negative effects of oxidized LDL cholesterol. Testing for the presence of lipid peroxides in urine will confirm that oxidative stress is present and that LDL cholesterol is more than likely becoming oxidized.

- Dietary factors that have been shown to raise LDL, such as saturated and trans fats, should be avoided. Exercise should be regular and consist of at least three aerobic and two anaerobic sessions per week. Exercise has been shown repeatedly to increase HDL levels-something that would improve the total cholesterol to HDL cholesterol ratio. Low HDL syndrome, or HDL levels that will not budge no matter what methods are used, will be addressed in future articles. Chronically low HDL levels have been shown in some studies to be a more important predictor of future myocardial events than high LDL or total cholesterol levels.[8,9]

- Lastly, the amino acid L-arginine should be taken at a dose of at least 5 grams (5,000 mg) per day in all patients with elevated LDL cholesterol. L-arginine supplementation will facilitate production of nitric oxide by eNOS and offset the negative actions of elevated caveolin. It should be noted, however, that when a person has elevated cholesterol, e.g., over 200 mg/dl or higher, they might have to increase the L-arginine dose toward the upper end of the dosage scale in order to obtain the desired increase in arterial nitric oxide production.[10] This higher arginine intake would amount to 15-20 grams per day in three to four divided doses. This dose has been shown to be safe and effective and should be strongly considered in these patients. Lower doses, at least in those with high total cholesterol, may not lead to improved arterial function.

In future articles I may address other important aspects of heart disease prevention and treatment.

References

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