Heart Health
Keep up with the beat

Nutrients for the Heart
A Healthy Diet and Lifestyle Are Your Best Weapons Against Heart Disease

Perspectives on Heart Disease
The Science Behind Preventing and Healing an Injured Heart
You Can’t Beat a Healthy Heart

AOR has a Wide Range of Cardiovascular Health Products
Heart Structure and Function 101

The Many Faces of Magnesium: The Secret Agent of Health

Curcumin Protects Against Heart Disease: New Research!

Vitamin K’s Role in the Maintenance of Healthy Arteries

The Importance of Nitrates in Reducing CVD

Cholesterol & Cardiovascular Disease Revisited: Myth or Merit

What You Need to Know About Mitochondrial Dysfunction and the Heart

Methylation & Homocysteine: Their Vital Roles in Heart Health
The heart is the most important muscle in the body. Yes, it is a striated muscle that functions and contracts similarly to an arm muscle, or a leg muscle. However, as we know, it has the very unique ability to contract tirelessly at a constant beat, pushing blood, oxygen and nutrients to the rest of our muscles, tissues and cells so that the body can function as a whole unit.

The heart is made up of two very important systems: these can be thought of as an electrical system and a plumbing system. The electrical system is comprised of various nodes, or “switches,” and fibres, or “wires.” When activated, the switches or nodes send an electrical current down the wires or fibres; these fibres then affect the electrolyte concentrations in the tissues, resulting in a muscular contraction.

The Electrical System of the Heart
There is a small nerve-rich area just above the right atrium called the sinoatrial (SA) node (see Figure 1). This node is the original pacemaker, initiating its own electrical impulse that causes both atria to contract. This “electrical shock” squeezes the atria, forcing blood through the one-way valves into the ventricles. The electrical impulse then travels to another node called the atrioventricular (AV) node, where the impulse is briefly delayed while the atria finish emptying into the ventricles. Then the AV node quickly transmits the signal to another bundle of nerve fibres called the Bundle of His, and subsequently into fibres that surround the right and left ventricles called bundle branches and Purkinje fibres, causing the ventricles to squeeze blood out into each of the coronary arteries, the pulmonary artery and the aorta. Then, the same process begins all over again, occurring an average of 60-80 times per minute at rest in a healthy person.

The electrical system is a complicated but fascinating phenomenon. It is governed by the exchange of minerals called electrolytes into and out of the cell. The main electrolytes in the body include sodium, potassium, chloride, calcium and magnesium. With the exception of the SA node, a nerve impulse is generated when a hormone stimulates a nerve cell, activating the exchange process of these electrolytes from one end of the nerve cell to the other and then into the next cell in a chain reaction.

Electrolyte availability can heavily influence nerve signals and muscular effects. Sodium, potassium and chloride regulate nerve signal transmission. Calcium and magnesium regulate the resulting contraction and relaxation of a muscle. Too much or too little of any of these electrolytes can cause erratic signals and contractions, either directly in the heart or in the blood vessels.

The Plumbing System of the Heart
Now that we basically understand what initiates heart contractions, let’s look at where and how blood moves. When blood is forced by pressure from the pumping of the heart through the arterial system of the body, it delivers oxygen and nutrients to tissues. The blood accepts carbon dioxide and cellular waste from the tissues and then enters the venous system to dispose of this waste through the liver, kidneys and lungs and then return to the heart. The veins
Ions and minerals are vital to healthy nerve signal transmission and muscle contraction and relaxation. Deficiencies, overloads or imbalances of any of these minerals can lead to erratic nerve impulses, which can cause arrhythmias, and modifying arterial tension. As previously discussed, such minerals include magnesium, potassium, sodium, and calcium.

Cellular Metabolism

General cellular metabolism depends on nutrition. Not only is getting sufficient energy important, but getting sufficient nutrition is equally if not more important! Getting the right nutrients gives cells what they need to make what the body requires to operate normally. Many vitamins and minerals and amino acids, for example the B-complex or magnesium, serve as co-enzymes for various metabolic reactions including energy breakdown or synthesis, methylation, homocysteine metabolism, and countless others (see Figure 2).

Blood Vessels are Muscles, But They’re Part of the Plumbing System Too

There are several types of muscles. It was already mentioned that the heart is a striated muscle, just like the main arm and leg muscles that help us move. Blood vessels, however, are also made up of a type of muscle tissue called smooth muscle. These muscles also contract and relax, which in part helps regulate blood pressure. However, they can get blocked up by accumulating plaque or by a clot, just like a plumbing system can get clogged due to an accumulation of junk on the tube walls or due to a blockage. Plaque in the arteries is like a scab on the skin that results in a scar. It is an aggregation of immune cells, calcium and fatty substances like cholesterol that rush to the site of injury in an attempt to heal the tissue. If the site is reinjured, the scab gets bigger, blocking the artery, or a scar may form, making the tissue less flexible and therefore less functional.

What Does Nutrition Have To Do With It All?

Endothelial Health

The fact is that more and more evidence is pointing toward healthy blood vessels being first and foremost in cardiovascular health. Blood vessel damage can cause plaque build-up, reduced vessel flexibility, reduced energy production by endothelial cells, and a compromised ability to heal. Getting the right nutrients ensures that blood vessels remain healthy and able to function and recover from injury appropriately. Some of these nutrients include vitamin C, nitric oxide, amino acids and antioxidants.

Blood Clotting

The ability of the blood to clot normally is a huge health factor. Abnormal blood clotting can lead to either thickening or thinning of the blood, both of which are dangerous. Most clotting factors are immune cells of some sort. By modulating the production and activity of these clotting factors, certain well-known nutrients like vitamin K encourage healthy blood clotting, while others like omega-3 fatty acids and vitamin E promote thinning of the blood, and still many other nutrients have less well-known effects on the blood.

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The Right Nutrients in the Right Amounts at the Right Time

True Orthomolecular Medicine

Of course, we all know that eating the right foods is an integral part of keeping the cardiovascular system healthy. However, it is even more beneficial to get the optimal forms of nutrients when they’re needed the most in adequate quantities to best support the body.
Magnesium is one of those supplements that is very well known for its benefits throughout the natural health community. However, one of the problems with magnesium’s almost celebrity status is that the details of the multiple benefits that it has to offer are often overlooked and underappreciated. This article explores the key role that magnesium plays in a number of disease processes. Additionally, it will highlight the benefits of certain often overlooked magnesium compounds (chelates), which complement magnesium by exerting their own beneficial effects.

**Magnesium is Vital**
Magnesium is involved in over 300 biochemical processes in the body. One of its most important functions is that it plays a key role in producing energy (see Figure 1). This makes it vitally important for all cellular functions and processes. It helps maintain normal muscle and nerve function, keeps heart rhythm regular, supports a healthy immune system, and keeps bones strong. The problem with this essential mineral is that most people do not have sufficient levels for optimal health.

A gradual depletion of nutrients from our soils has left many vegetables with lower levels of magnesium. Despite eating a healthy and well-balanced diet, a person can develop low magnesium levels over time. A dietary survey suggests that many North Americans do not get the minimum recommended amounts of magnesium daily. Even though the classic symptoms of magnesium deficiency are rare, health issues can occur well before an overt deficiency. A good analogy is a rusty versus well-oiled wheel. A constant low level of magnesium will still allow the rusty wheel to turn but it will be slower and require greater effort. The same can be said about cellular energy production if magnesium levels are below optimum levels.

**Causes of Magnesium Deficiency**
Another factor that contributes to magnesium deficiency is that it is often depleted by various common conditions and medications. Since magnesium is absorbed in the small intestine, conditions such as Crohn's disease, intestinal surgery, gluten sensitivity (celiac enteropathy)2 and other health problems can impair absorption. Frequent diarrhea and vomiting can also cause depletion. Irritable bowel syndrome is the most common disorder diagnosed in North America and it can often cause loose stools and intestinal spasms, which can contribute to further magnesium excretion in addition to impairing absorption.

Many commonly used medications, such as proton pump inhibitors, diuretics and antibiotics cause magnesium depletion.3,4 Some of these drugs are taken for a long time, which can create a deficiency over that time. This is especially concerning when many elderly are on multiple medications for a number of years. Older adults are at an increased risk for magnesium deficiency since intestinal absorption of most
nutrients can decrease with age. They also have lower intakes than younger adults and often have increased excretion. The combination of a diet with low amounts of magnesium, poor intestinal absorption due to intestinal damage and prescription drug use can all contribute to chronically low magnesium levels.

**Low Magnesium Levels Linked to Poor Health**

Considering the pivotal role that magnesium plays in cellular signaling, function and energy production, it is no surprise that a deficiency has a broad impact on multiple organ systems and has been linked to numerous health conditions. Additionally, supplementing with magnesium has also been shown to have positive results in a number of pathologies. The following is a selected list of key conditions that magnesium has been studied to have a beneficial effect on.

**Cardiovascular disease:** A recent review found a significant inverse correlation between serum magnesium and incidence of cardiovascular diseases. Low magnesium levels have been implicated in inflammation and endothelial dysfunction. This pro-inflammatory state is believed to disrupt the arterial lining and promote thrombosis, which leads to atheroma formation and atherosclerosis, hypertension, and vascular calcification. Furthermore, magnesium also inhibits HMGCoA reductase, the rate-limiting enzyme for cholesterol synthesis (much like the statin class of drugs). Therefore it can reduce low-density lipoprotein (LDL).

**Hypertension:** Magnesium causes vascular smooth-muscle cell relaxation by acting as a mild calcium blocker and reduces angiotensin-induced aldosterone synthesis, which can lower blood pressure. A recent meta-analysis found that magnesium supplementation showed an average decrease in systolic blood pressure of 3-4 mmHg and diastolic of 2-3 mmHg. Additionally, people taking diuretic medications for hypertension can have higher magnesium excretion, so they have an additional need for supplementation.

**Diabetes:** Magnesium is commonly deficient in many type 2 diabetics due to loss through the urine. Low intracellular magnesium has been linked to impaired insulin action, insulin resistance and inflammation. Considering the importance of magnesium in hypertension, low magnesium levels are most likely a key factor in metabolic syndrome as well. Since diabetics are at a higher risk of cardiovascular disease and magnesium is essential for the proper function of insulin, they have a greater need for adequate magnesium levels.

**Other disease processes linked to improvements with magnesium supplementation** include atrial fibrillation, cardiac arrhythmia, osteoporosis, kidney stone prevention, chronic pain, stroke recovery, fibromyalgia, chronic fatigue syndrome, headaches, ADHD, asthma, non-alcoholic steatohepatitis (NASH), premenstrual syndrome and menstrual cramps to name a few. Interestingly, magnesium is also required for the conversion of the active form of vitamin D. A deficiency of magnesium can impair the production of vitamin D which like magnesium has a myriad of health benefits.

**Choosing Among Magnesium Supplements**

As a supplement, magnesium is most commonly found in...
small amounts in multivitamins and in certain over the counter laxatives. Minerals such as magnesium or calcium are combined with another molecule to stabilize the compound. Each combination (such as magnesium citrate) has different absorption, bioavailability and therapeutic value. These additional molecules can really impact the medicinal value of the magnesium, and some even have beneficial effects in their own right.

There are a number of different forms of magnesium available on the market. The most common forms and their benefits are listed below.

**Magnesium oxide:** Often used in milk of magnesia products since this form has a strong laxative effect. Even though this combination contains a large proportion of magnesium compared to the oxide molecule, it has poor bioavailability and readily causes loose stools, therefore it is considered the least optimal form to use as a supplement.

**Magnesium sulfate:** This form is often used as an intravenous preparation but it is not used in oral formulations. Since it does have some absorbability through the skin, it is also found in Epsom bath salts.

**Magnesium citrate:** A commonly used form that has good bioavailability compared to oxide. It is also very rapidly absorbed in the digestive tract but it does have a stool-loosening effect. This form is found in many supplements and remains a solid option for delivering magnesium into the body.

**Magnesium aspartate:** This form has increased bioavailability compared to oxide and citrate. There were some promising clinical trials conducted in the 1960s that found a combination of magnesium and potassium aspartates had a positive effect on fatigue and they reduced muscle hyper-excitability. Physiologically this makes sense since both magnesium and aspartic acid are critical players in cellular energy production. This form is not commonly found but has been used for chronic fatigue syndrome.

**Magnesium glycinate:** Glycine is a well known calming amino acid. This combination has good bioavailability and it does not have a laxative effect since glycine is actively transported through the intestinal wall. Due to the calming and relaxing effect of both glycine and magnesium, this combination has been used successfully for chronic pain and muscle hypertonicity.

**Magnesium malate:** This little-known combination has been studied for use in fibromyalgia. Since malate is a substrate in the cellular energy cycle, it can help improve ATP production, and there is some preliminary evidence that it may reduce muscle pain and tender points in fibromyalgia patients.

**Magnesium orotate:** This is another relatively unknown chelate combination containing orotic acid. This form has good bioavailability has had been studied specifically for heart health. Orotates can penetrate cell membranes, enabling the effective delivery of the magnesium ion to the innermost layers of the cellular mitochondria and nucleus. Orotates themselves increase the formation of RNA and DNA which can help heart cells repair and therefore improve function. The combination has been shown to improve heart failure, symptoms of angina and exercise performance in clinical trials. Additionally, low levels of vitamin B6 have been shown to further deplete both magnesium and taurine.

**Magnesium taurate:** Both magnesium and the amino acid taurine share the ability to improve cardiac function, both have a potentiating effect on insulin sensitivity and both have calming effects on neuromuscular excitability. The actions of both have striking similarities when it comes to cardiovascular health. They both have blood pressure reducing effects, stabilize nerve cells, improve the contraction of the heart muscle and have an anti-thrombotic effect. Additionally, low levels of vitamin B6 have been shown to further deplete both magnesium and taurine.

A note on potassium: When there is a magnesium deficiency there often can...
be a concurrent potassium deficiency. A major function of potassium is to maintain the excitability of nerve and muscle tissue; together with magnesium it plays a key role in maintaining a stable and regular heart rhythm and muscle contraction. Both of these key minerals can become deficient in chronic alcoholism, diabetes (type 2), severe vomiting and diarrhea and with the use of diuretic drugs. Therefore, if there is a magnesium deficiency present, consider potassium levels as well.

**Concluding Thoughts on Magnesium**

Due to its broad ranging beneficial effects, magnesium has really emerged as a quintessential health supplement with an excellent safety profile. Very few natural ingredients have such a large body of compelling evidence for their use. As with vitamin D, it would be prudent to assess your intracellular levels to address any deficiency that may be present. Our diet and lifestyle unfortunately predispose many people to developing an insidious deficiency of this essential mineral. Many health conditions can benefit from magnesium supplementation to restore optimal cellular function and energy production. Various forms of magnesium can be employed for specific health concerns and to increase bioavailability. Even though magnesium can often get overlooked for more vogue or popular supplements, the overwhelming benefits speak for themselves, thus making it a "not-so-secret agent" in your quest for optimal health.

**Box 2. Healthy food sources of Magnesium**

<table>
<thead>
<tr>
<th>Foods rich in Magnesium</th>
<th>Calories</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pumpkin seeds, raw</td>
<td>187</td>
<td>22</td>
</tr>
<tr>
<td>Spinach, boiled</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>Swiss chard, boiled</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Soybeans, cooked</td>
<td>298</td>
<td>12</td>
</tr>
<tr>
<td>Salmon, chinook</td>
<td>262</td>
<td>11</td>
</tr>
<tr>
<td>Sunflower seeds, raw</td>
<td>205</td>
<td>8</td>
</tr>
<tr>
<td>Sesame seeds</td>
<td>206</td>
<td>8</td>
</tr>
<tr>
<td>Halibut, baked/broiled</td>
<td>159</td>
<td>6</td>
</tr>
<tr>
<td>Black beans, cooked</td>
<td>227</td>
<td>6</td>
</tr>
<tr>
<td>Navy beans, cooked</td>
<td>258</td>
<td>6</td>
</tr>
</tbody>
</table>

**References**

Curcumin is the bright orange coloured major active compound extracted from the spice turmeric. Turmeric is a widely used condiment in South East Asia and is a favoured component of Indian curries. The spice has been used for centuries in both Indian and Chinese cuisine as a flavouring and colouring agent and as a food preservative.

**Turmeric in Ayurvedic and Traditional Chinese Medicine (TCM)**

Turmeric is a key ingredient in many frequently used Ayurvedic and TCM formulas. In fact, turmeric is the main ingredient used by almost every Indian household for ailments such as digestive disorders, liver complaints, parasites, diabetes, kidney disease and various types of inflammatory conditions including arthritis. It is also used topically for infections and in cosmetic preparations. Typically, the turmeric spice is added to hot milk with ghee (clarified butter) and given in copious amounts to anyone with a sprain or a swelling due to an injury.

**Curcumin - The Active Ingredient**

Curcumin, the major active ingredient in turmeric, is widely studied for its effects on diabetes, cataracts, osteoarthritis, kidney disease, liver conditions like cirrhosis and bile duct disorders, psoriasis, neurodegenerative conditions including Alzheimer’s and Parkinson’s, a host of cancers such as colon, breast, liver, prostate, bladder, skin and many others.

Research on curcumin in universities all over the world is prolific; within the last thirty years, probably no other natural product has been the subject of more animal and human research than curcumin. Curcumin has been demonstrated to be a powerful antioxidant and anti-inflammatory agent in numerous scientific studies. More than twenty different pathways of cancer protection have been established. Recently, researchers have looked into why Ayurvedic physicians have used turmeric in their formulas for heart health.

**Curcumin and Heart Research**

**Animal Studies on Curcumin and Heart Health**

Researchers at the universities of Tokyo and Toronto independently suggested that curcumin may be beneficial for heart health. The Toronto researchers used an animal model that mimicked high blood pressure in humans (by deliberately reducing the flow of blood in the aorta- the large blood vessel) and found that those animals subjected to such conditions quickly developed an enlarged heart and subsequent heart failure. However, those animals subjected to the same conditions but given a daily dose of curcumin in their diet were protected from enlargement of the heart and did not end up having heart failure.

Similarly, researchers in Tokyo using a different model of high blood pressure (they used animals that spontaneously developed high blood pressure due to salt in their diet) were also protected from heart enlargement and heart failure by having curcumin in their daily diet. Heart enlargement is a common feature of high blood pressure. The heart has to work that much harder to pump the blood, and like any other muscle when over exerted will increase in size, but in the case of the heart this isn't good and is normally associated with poor health and increased risk of death.

Both set of researchers were able to meticulously work out the protective mechanism of curcumin. In short, curcumin inhibits a key class of enzymes called the Histone Acetyl Transferases (HATs) for short, that normally function to increase the expression of inflammatory proteins. This way, inflammatory damage, as well as enlargement of the heart and heart failure are reduced. The pathology of the animal’s heart shows that curcumin also protects against fibrosis or scarring of the heart tissue. Scarred tissue is damaged tissue and is thus unable to perform the normal physiological function, which in the case of the heart is as a pump.

**Human Studies on Curcumin and Heart Health**

Since 2008 when the two animal studies were published, some human clinical data has emerged supporting the use of curcumin for heart and blood vessel health. The first was a study from Thailand which looked at the effects of a curcumin mixture given to patients that suffered a recent heart attack following coronary artery bypass. There were 121 patients who were given 4g of curcumin and whom underwent various tests.

The researchers found that curcumin decreased the incidence...
of future heart attacks by over two and half times compared to patients not receiving any curcumin. Furthermore, the incidence of left ventricular dysfunction (a measure of the damage to the heart) was significantly reduced again in the curcumin group, this time by nearly nine times! These results are hugely significant! Other biological markers of heart disease such as inflammation (C-Reactive Protein, CRP) were also greatly reduced.

Another human study from Japan used a much smaller daily dose of curcumin, just 25mg given to 11 postmenopausal women who were either exercising or not exercising were given the curcumin dose for eight weeks. The researchers looked at a specific marker of vessel health called Flow Mediated Dilation (FMD) which is a very sensitive marker and predictor of future cardiovascular events, with every 1% decrease in FMD being associated with a 12% increase of cardiovascular risk.

A daily dose of 25mg significantly improved FMD similar to the exercise group. In other words, curcumin provided the same health benefit as exercise. The researchers concluded that curcumin could act as an alternative for patients unable to exercise!

A second follow-up study by the same Japanese group also reported a reduced left ventricular afterload (this is the pressure the heart has to pump against) compared to the group not taking curcumin.

It is worth pointing out the large discrepancy between the 4g per day in the Thailand study compared to the 25mg in the Japanese study. Curcumin has poor bioavailability: that is, very little reaches the site of action due to a number of issues. Curcumin has poor solubility, low stability, rapid degradation by enzymes, as well as fast elimination from the body.

A More Bioavailable Curcumin Extract

The Japanese used a super bioavailable extract of curcumin with considerably higher bioavailability than the regular curcumin. Much attention has been devoted to improving bioavailability and thus reducing the daily dose. Current literature search suggests the formulation that has the highest bioavailability by far is the Longvida® product, over 100 times compared to regular curcumin. In contrast, the Japanese product used in the study is reputed to be about 30 times more bioavailable.

The Longvida® curcumin was specifically developed by the scientists at UCLA (University of California in Los Angeles) after studying over two hundred different formulas. The unique delivery system used in Longvida® curcumin is called a solid lipid nanoparticle that not only improves the solubility and stability of the curcumin but also prevents degradation by the enzymes that normally help keep out any foreign substances.

Conclusions

Curcumin has been used by ayurvedic practitioners for centuries, but only recently have human studies been conducted and the mechanism been studied. This versatile molecule offers exciting possibilities in heart health and will be increasingly used in natural health products.

References

Advances

Vitamin K2’s Vital Role in the Maintenance of Healthy Arteries

Having healthy arteries certainly has something in common with having healthy bones; both organs depend on vitamin K2 to regulate the deposition of calcium in them. Relatively recent research has revealed more about how vitamin K2 level can be an indicator of the health of both your arteries and bones. Clinical studies have demonstrated that low levels of vitamin K2 are associated with an increased risk of having heart disease and atherosclerotic plaque development.1

Vitamin K Basics

Vitamin K1 (phylloquinone) is found in plants including green leafed vegetables; it has less bioavailability than vitamin K2. Vitamin K2 (menaquinone) is present in dairy, egg yolks, and organ meats. In supplements, the most commonly used forms are MK-4 (menatetrenone/menaquinone-4) which is synthetic and is also produced by bacteria in the human body, and MK-7 (menaquinone-7) which is found in the fermented soy food natto. Vitamin K1 is metabolized to MK-4 inside the body, suggesting that this is the form that the body actually uses.

The liver requires vitamin K in order to make blood clotting proteins, and as this article discusses, for the regulation of calcium deposition. The vitamin K2 menaquinones comprise approximately 10% of vitamin K; menaquinone exists naturally in the body in several different forms ranging from MK-3 to MK-13.

How Can Calcium Accumulate in the Arteries?

When calcium is lacking in the bone, it is frequently observed in excess in the arteries and vice versa, this has been established for quite some time in the medical community. However, earlier on it was not fully understood what processes were at work to cause abnormal calcium deposition in the arterial system, or a lack of normal calcium deposition where it should be occurring, in the bones. A lack of calcium in the bones leads to osteoporosis, a condition where the bones become porous and brittle; whereas coronary heart disease can result from calcium deposition in the arteries and reduce the ability of blood to flow. Vitamin K has already received plenty of attention for its role in promoting healthy blood clotting; however, there is not enough awareness of the amount of vitamin K2 needed to maintain healthy arteries and bones. Many people are not getting the amount of vitamin K necessary to support a healthy cardiovascular system, which is believed to be greater than 32mcg per day according to a clinical study.1

The Discovery of Arterial Plaque

In the 19th century, an unknown material resembling bone was discovered in the linings of diseased arteries. Abnormal calcium deposits are found in the lining of the arteries (the intima), the arterial muscle layers, and also the in the heart valves. Scientists questioned what was controlling the deposition of this material in the body. Later on, a protein was found by Dr. Linda Demur (at the University of California in Los Angeles) in human arterial tissue that was previously thought to only have existed in bone tissue; this protein called morphogenetic protein-2 has an important function in influencing the formation of bone.2 Since that time, a number of bone calcium regulators have been found in atherosclerotic plaque tissues, such as osteopontin and matrix GLA-protein, proving that both arterial and bone health are related, and interestingly they are both regulated by similar influences.3

What Do Bones and Arteries Have in Common?

Although patients with vascular disease and osteoporosis may share many characteristics in common such as a sedentary lifestyle, smoking, diabetes and high cholesterol, abnormal calcium deposition in the arteries has been observed even in apparently healthy people.2 Both the bones and the arterial system have their own regulation mechanisms, therefore it is clear that there are other processes occurring to cause abnormal calcium deposition in the arteries in the case of diseased arteries. Prescription drugs such as alendronate (Fosamax) and raloxifene (Evista) are able to increase calcium deposition in the bones, however they do not stop the formation of calcium plaques in the arteries. Research...
is continuing to demonstrate that vitamin K is able to influence calcium metabolism in the body by promoting deposition in the bone and at the same time prevent it from accumulating in the arteries. A Japanese study conducted over a two year period investigated vitamin K2’s ability to improve bone health in osteoporosis patients. It found that vitamin K2 supplements reduced spine fractures by 52% in these patients as compared to those that did not get the treatment of 45mg/day. Although this dose which is typical for osteoporosis treatments is relatively high, lower dosages have also proven to provide substantial benefits. 

**Clinical Studies Prove the Vitamin K Connection to Arterial Health**

A large scale clinical trial carried out in Holland starting in 2004, the Rotterdam Heart Study, proved that vitamin K2 levels are intimately related to heart disease. A total of 4800 participants were tracked for seven years to determine the effect that vitamin K2 had on their cardiovascular health. Both MK-4 and MK-7 were used in the study, but not analyzed separately. The study concluded that those who had the highest intakes of vitamin K2 had a reduced risk of death from heart disease by 57%, over those that had the lowest intake levels. It is important to note that this relationship was not observed with vitamin K1. The higher intakes of vitamin K2 corresponded with a decreased amount of calcium in the aorta, this being an indirect measurement of atherosclerosis. Moderate to severe calcification was observed in those participants that had the least amounts of vitamin K intake. Heart attack and aortic calcification risk was lowest if an amount greater than 32.7 mcg per day of vitamin K2 was taken. Another Dutch cross-sectional study at the Julius center for Health Sciences involved 564 post menopausal women, 360 of whom already had coronary artery calcification. The effects of both vitamin K1 and vitamin K2 (mk-4-mk-10) were compared; it was determined that the vitamin K2 reduced levels of coronary artery calcification.

**Vitamin K2 is an Essential Heart Heath Nutrient**

In conclusion, abnormal calcium signaling is therefore responsible for contributing to atherosclerotic plaque growth, and vitamin K deficiency is now believed to promote this occurrence. The present recommended dosages of 120 mcg/day for men and 90 mcg/day for women may not be high enough to ensure that optimal heart and bone health are maintained. Ensuring that you are receiving adequate levels of vitamin K may be one of the best things you can do for your heart!

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**References**


**Additional References**

Advances

In the late 1960’s researchers discovered a naturally produced “factor” that would relax the blood vessels. They named it endothelium derived relaxing factor (EDRF). After considerable research, it was later discovered that EDRF was a simple molecule containing one atom of nitrogen and one atom of oxygen produced locally by the blood vessels, and was more correctly called nitric oxide (NO). This discovery eventually culminated in three researchers winning the Nobel Prize for medicine in 1998; sadly one of the key researchers, Salvador Moncada, was overlooked by the Nobel Committee. Who says there are no politics in science?

Cardiovascular Disease (CVD), which includes high blood pressure (hypertension), angina (ischemia), arterial damage (atherosclerosis), stroke and heart attack is still the number one cause of suffering and death world-wide. One in three Americans and Canadians are affected by CVD, and over a billion people are affected by high blood pressure alone. The costs associated with CVD are quite staggering, with a 2006 cost estimated in Western Europe to be over 200 billion Euros.

Government Initiative to Lower Cardiovascular Disease

In recognition of these alarming statistics, there is a serious initiative on the part of governments to promote the increased intake of fruits, vegetables and fiber along with increasing physical activity. The recommended consumption of fruits and vegetables has been upgraded from five daily servings to nine in North America. Various studies of large populations have repeatedly and clearly reported a lower incidence of CVD in correlation with a higher intake of fruits and vegetables. These findings have culminated in the famed Dietary Approaches to Stop Hypertension (DASH) study. The DASH study was specifically designed to lower blood pressure and recommends eight to ten servings of fruits and vegetables a day, along with consumption of low-fat dairy products. The results of the DASH diet (see Figure 1) in reducing blood pressure have been found to be as effective as some prescription drugs for lowering blood pressure!

Researchers from John Hopkins University in Baltimore reported an 18% reduction in a 10 year risk of heart disease with the DASH diet. The researchers stated that, “In addition to reducing blood pressure, the DASH diet should substantially reduce the risk of coronary heart disease”.

Similarly, the lower incidence of CVD in patients on the Mediterranean, vegetarian, and Japanese diets has been associated with a high fruit and vegetable intake. In fact, some researchers have reported that the greatest protection against CVD is offered by diets with the highest content of leafy green vegetables.

This has led scientists to ask an important question, “What is the common factor in such diets, and therefore the key CVD protective compound(s)? It appears that the riddle has been finally solved. A group of researchers from Sweden, the UK, and the US have independently and collaboratively shown that the nitrates and nitrites in fruits and vegetables may be the answer, and have forwarded convincing evidence to support their hypothesis.

Inorganic Nitrates the Answer?

Nitrates can be classified into two categories, organic and in-organic. Organic nitrates are what most of us are familiar with e.g. glyceryl trinitrate (GTN) – the tiny tablets usually dispensed by pharmacists in glass vials and recommended to be placed under the tongue for pains due to angina, or isosorbide di-nitrate a more upgraded and stable form of GTN. These organic nitrates have been in use in medicine since the mid-1800s. Then there are the in-organic nitrates like potassium or sodium nitrate which are commonly found as salt forms in soils, rocks and plants; they have been used for thousands of years, from the manufacture of gun powder to food preservation, and for heart ailments by early Chinese physicians.

Researchers have looked at various commonly consumed western vegetables and their nitrate/nitrite content. As can been seen from Table 1 on pg. 16, the
vegetables with the highest nitrate/nitrite content are spinach, cabbage, beet root, collard greens, leeks etc. Nathan Bryan at the University of Texas, and colleagues investigated the nitrate/nitrite content of various herbs and vegetables consumed in the West and by the Eastern cultures. Indeed, certain herbs with the highest nitrate/nitrite content are associated with a reduction in CVD. For example, the herb Radix miltiorrhizae has a high nitrate content and is widely used in Traditional Chinese Medicine (TCM); known as Dan Shen, for conditions such as angina, heart attack and stroke. The herb’s protective effect on the heart is recognized due to its ability to dramatically raise NO levels. Clinical studies have found Dan Shen almost comparable to nitroglycerin, and yet without the tolerance that normally develops with most organic nitrates. Inorganic nitrates seem to be free of this restriction.

Until the mid-1990’s, researchers believed that the only way to increase NO levels was by the conversion of the amino acid L-arginine into NO, with the help of various enzymes which require the presence of oxygen.

**Discovery of a new pathway!**

In the mid-1990’s, researchers from the UK and Sweden discovered a new pathway for NO generation from dietary nitrates. The Swedish researchers led by Jon Lundberg, Eddie Weitzberg, and Nigel Benjamin from London, were trying to find out why diets like the Mediterranean, vegetarian, Japanese or the DASH diet were particularly protective of the heart. Both groups independently reported that the composition of leafy green vegetables, a key component of all these diets, was the high nitrate content. The researchers proposed that the nitrate was converted into NO via a reductive process that did not require any enzymes or the presence of oxygen. (see Figure 2 on pg. 16)

Systolic blood pressure above 115 mmHg is the most important determinant of the risk of death, responsible for 7-8 million worldwide deaths annually. Indeed, it has been suggested that, in moderate hypertensive patients, just a 5mmHg reduction in blood pressure might reduce the incidence of stroke by 22% and coronary heart disease by 16%.

The beneficial effect of fruits and vegetables on blood pressure is well known. Comparison of the effect of traditional Japanese diet, which has a nitrate content and a diet with low nitrate content (20 fold less) in the same 25 subjects (a cross-over study), demonstrated a significantly lowered diastolic blood pressure (DBP) of 5mmHg in the nitrate rich diet.

Because vegetables are naturally rich in nitrates, it seems reasonable to investigate if inorganic nitrate alone, corresponding to the same amount present in a single serving of a plate of salad, could affect blood pressure in healthy subjects. Jon Lundberg and Eddie Weitzberg’s group in Sweden tested their hypothesis in a small double-blind placebo-controlled, cross-over designed study. A small dose of sodium nitrate was administered to adults for three days after which blood pressure was measured. Indeed, DBP was reduced by 4mmHg compared to placebo (sodium chloride providing an equivalent amount of sodium). The rise in blood nitrate levels was accompanied by a fall in blood pressure. This suggested that the blood pressure
lowering effect was due to the nitrate being converted into nitrite and then into NO (see Figure 3).

Although such changes in blood pressure appear relatively small, it must be remembered that the dose used is equivalent to the nitrates found in only a single serving of salad (approximately a plate of 250 g). These results become more meaningful in the reduction of mechanical shear and stress to the vascular endothelium over the entire lifetime of the individual. As well, the study was conducted in normotensive patients that were otherwise healthy. It is expected that a significantly greater fall in blood pressure would occur in hypertensive patients. Finally, the study was only three days long!

Following up on this important finding, Amrita Ahluwalia and her group at St. Bart's Hospital, University of London, conducted an elegant study to prove the point that nitrate-rich vegetables can reduce blood pressure via conversion into NO via nitrite. Again in a double-blind randomized placebo-controlled study, healthy adult volunteers were given 500mL of beetroot juice to drink.14 The amount of nitrate present was three times the amount administered in the Lundberg study. Three hours later there was a significant reduction in SBP of 10 mmHg and DBP of 8 mmHg. The beauty of this study was that it demonstrated cause and effect. By monitoring plasma nitrate and nitrite levels and blood pressure, the researchers demonstrated that raised plasma nitrate and nitrite levels corresponded with a decrease in blood pressure.

Several points were raised in this study. First, there is a small delay of a half to one hour or so that occurs in blood pressure reduction after the intake of juice; this represents the time taken for conversion of nitrate into nitrite by the bacteria in the mouth and then the conversion of nitrite into NO in the stomach. Second, the study demonstrates a dose-response relationship, the higher the dose the greater the effect. Finally, a clear relationship was established between raised plasma levels and blood

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Table 1. Nitrate and nitrite contents of vegetables (adapted from Wang et al. 2000)

<table>
<thead>
<tr>
<th>Vegetable types and varieties</th>
<th>Nitrate mg/100 g fresh weight</th>
<th>Nitrite mg/100 g fresh weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Root vegetables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrot</td>
<td>0.002–0.023</td>
<td>92–195</td>
</tr>
<tr>
<td>Mustard leaf</td>
<td>0.012–0.064</td>
<td>70–95</td>
</tr>
<tr>
<td><strong>Green vegetables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettuce</td>
<td>0.008–0.215</td>
<td>12.3–267.8</td>
</tr>
<tr>
<td>Spinach</td>
<td>0–0.073</td>
<td>23.9–387.2</td>
</tr>
<tr>
<td><strong>Cabbage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese cabbage</td>
<td>0–0.065</td>
<td>42.9–161.0</td>
</tr>
<tr>
<td>Bok choy</td>
<td>0.009–0.242</td>
<td>102.3–309.8</td>
</tr>
<tr>
<td>Cabbage</td>
<td>0–0.041</td>
<td>25.9–125.0</td>
</tr>
<tr>
<td>Kale</td>
<td>0.364–0.535</td>
<td>76.6–136.5</td>
</tr>
<tr>
<td><strong>Melon</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wax gourd</td>
<td>0.001–0.006</td>
<td>35.8–68.0</td>
</tr>
<tr>
<td>Cucumber</td>
<td>0–0.011</td>
<td>1.2–14.3</td>
</tr>
<tr>
<td><strong>Nightshade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggplant</td>
<td>0.007–0.049</td>
<td>25.0–42.4</td>
</tr>
</tbody>
</table>

Classification of vegetables in terms of their nitrate content (adapted from Santanaria P., 2006)

<table>
<thead>
<tr>
<th>Nitrate content (mg/100 g fresh weight)</th>
<th>Vegetable varieties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low, &lt;20</td>
<td>Artichoke, asparagus, broad bean, eggplant, garlic, onion, green bean, mushroom, pea, pepper, potato, summer squash, sweet potato, tomato, watermelon</td>
</tr>
<tr>
<td>Low, 20 to &lt;50</td>
<td>Broccoli, carrot, cauliflower, cucumber, pumpkin, chicory</td>
</tr>
<tr>
<td>Middle, 50 to &lt;100</td>
<td>Cabbage, dill, turnip, savoy cabbage</td>
</tr>
<tr>
<td>High, 100 to &lt;250</td>
<td>Celeriac, Chinese cabbage, endive, fennel, kohlrabi, leek, parsley</td>
</tr>
<tr>
<td>Very high, &lt;250</td>
<td>Celery, cress, chervil, lettuce, red beetroot, spinach, rocket (rucola)</td>
</tr>
</tbody>
</table>
pressure reduction. Scientists love to show a physiological cause and effect relationship - this study does this!

A second study by Ahluwalia’s group showed that the blood pressure effect could be achieved with a lower intake of 250mL beetroot juice. More importantly, the effects of dietary nitrate from beetroot juice can be sustained over a longer period. The blood pressure effect lasts for over 24 hours!

Lundberg and Weitzberg’s group, using elaborate animal hypertensive models, have shown that nitrates can reduce blood pressure. In one model, blocking the NOS enzyme (responsible for NO production) with specific inhibitors of the enzyme caused hypertension in the animals. This effect was reduced by administering nitrites in the drinking water.

In a more recent 2011 study, the Swedes have used another model of high blood pressure (caused by removing the kidney) to show that nitrates not only reduced the blood pressure, but also reduced the fibrosis (scarring) and other damage caused in the animals. Furthermore, a much lower dose of nitrite that did not reduce blood pressure still protected against kidney damage, suggesting the use of a much lower dose as a preventive measure. More studies are needed on this exciting topic.

Other CVD protective effects of nitrates/nitrites/NO
Inorganic nitrates have been shown to have numerous cardiovascular protective effects including: endothelial function, platelet function and metabolic syndrome.

1. Endothelial function
The human vasculature is the largest organ in the body. The endothelial cells line the largest blood vessel, the aorta, to the tiniest blood capillaries. The endothelium is one cell thick and plays an important role in the health of the vessel. Any abnormality or damage to these cells therefore leads to endothelial dysfunction which may be the initiating factor in the pathology of CVD.

Endothelial cells are one of the key sites in the body where NO is synthesized. NO acts as a local hormone to the neighbouring cells, thereby monitoring the local environment. NO diffuses to the smooth muscle cells located directly beneath the endothelial cell lining causing vasodilatation or widening of blood vessels. Excessive free radicals will often “mop” up the NO resulting in the loss of the ability to execute vasodilatation which is not a good thing.

Animal studies with genetic knockout mice, lacking the enzyme that helps produce NO, are highly prone to cardiovascular complications. Nitrite supplementation reduces such endothelial disturbances and prevents damage. The Ahluwalia study showed that beetroot juice could effectively reduce endothelial damage as assessed by various inflammatory markers like C-Reactive Proteins (CRP). Recently, a direct relationship between reduced endothelial damage and higher plasma nitrite levels has been established. So the data seems to be very supportive of nitrates/nitrites preserving endothelial function.

2. Platelet function
The main function of platelets in the blood is to amass at sites of damage, causing clotting. Platelets have an innate ability of “togetherness”. The role of platelet activation, adhesion and aggregation in atherosclerosis is well known.

Reduced platelet aggregation or “stickiness” may not only prevent inappropriate clumping of cells causing thrombosis or clots, but it also allows blood to flow more easily, reducing the burden on the heart. Modulation of platelet function is an important therapeutic strategy in preventing atherosclerosis. Both beetroot juice and...
potassium nitrate have been shown to prevent platelet aggregation.14

3. Metabolic Syndrome

In 1985, Reaven coined the term Metabolic Syndrome to represent a cluster of symptoms that often appear together and may have a common initiating or causative event. Obesity, hypertension, high lipid levels and diabetes are the ‘four horseman of the apocalypse’ that have targeted one quarter of the world’s adult population. These four risk factors collectively increase the risk of CVD.

Animal studies in knockout mice lacking the NOS enzyme gene (thus preventing NO formation) results in full-blown metabolic syndrome. Various researchers have suggested that metabolic syndrome may be due to a deficiency of NO. The addition of nitrate and/or nitrite to the drinking water of the animals protects the animals and significantly reduces the lipid and triglyceride levels as well as the incidence of diabetes and weight gain.16 These results present an intriguing possibility for preventing and/or controlling metabolic syndrome. However, human studies are warranted.

4. Ischemia

Ischemia is the lack of oxygen delivery to tissues due in part to partial or complete obstruction of blood flow. Angina and heart attack are examples of an ischemic event. When ischemia occurs, the tissue with an obstructed blood supply (and thus oxygen) suffers irreversible damage. Damage to the blood vessels restricts blood flow leading to poor circulation.

Nitrates and nitrites have been shown to reduce the damage to the tissues and thus improve the circulation, leading to improvement in the symptoms.21

Conclusion

Nitric oxide is a versatile and an important molecule that plays a major role in heart and blood vessel health. Since its recent discovery there has been tremendous research of how it is generated, its mechanism of action and its therapeutic potential. In the last ten years there has been an explosion in the research with clinical studies confirming its safety and its effectiveness.

References

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Additional References

Advances

Many people have the perception that all dietary fat is bad for your health. For years we have been trained and taught by the media, health professionals and even our friends and family that one of the most important things we can do to stay healthy and disease free is to avoid dietary fats. As we get older, often the first warning sign of cardiovascular disease that is flagged by our family doctor is elevated cholesterol. There is little disputing that cholesterol, particularly low density lipoprotein (LDL), has been called the driving force of atherosclerosis. However, there is emerging research that challenges the cholesterol hypothesis as the key-driving factor in heart disease.

The evidence supporting the cholesterol theory is based on the evidence that high total cholesterol (TC) and LDL are linked to increased numbers of cardiac event endpoints (i.e. a heart attack). This association may overlook a key factor associated with coronary heart disease (CHD). A number of studies have noted that half of the people admitted to the hospital with heart disease had low cholesterol levels. A recent review has shown that high cholesterol is a very weak, non-significant factor in CHD. Looking at cholesterol levels may be taking the focus away from the disease process really responsible for cardiac events, which is calcified plaque.

An accurate and direct way to assess the risk of CHD is the measurement of coronary plaque burden and progression. Assessment of coronary plaque burden via electron beam tomography (EBT) or coronary computed tomography (CT) angiography is a non-invasive measurement of coronary plaque burden. The factor that has been linked to increases in the risk of adverse coronary events is calcified plaque burden. More than 10 studies have not found a connection between coronary artery calcification (CAC) progression and TC or LDL levels. This suggests that cholesterol may not be the key-driving factor in atherosclerosis and cardiac events.

Based on the above evidence, it seems that cholesterol is not the primary culprit in heart disease. Therefore, lowering cholesterol as the first line of defence for preventing heart attacks and strokes for people with no history of cardiac events should be re-examined. A number of placebo-controlled trials have shown that statin medications do not effect the progression of CAC, despite lowering inflammation and stenosis. A re-examination of the evidence points to statins not having an impact on all cause mortality in cases where people do not have coronary heart disease.
It is important to note that statins have demonstrated a protective effect in those that have already experienced a heart attack or stroke. Some of the benefits of statins have been attributed to effects on inflammation or raising vitamin D levels rather than from lowering cholesterol.

If elevated TC and LDL have no (or very weak) association with CHD, the unanswered question remains: what is responsible for the high rates of cardiac events and death in North America? What is driving CAC? Consider the fact that the French population eats more fat than any western country (including Canada and the United States), but their incidence of heart-related death is less than half of that in North America. This further suggests that dietary fat is not the main cause of heart disease. The question then becomes, what is it about the standard North American diet, other than the high fat intake, that promotes heart disease? One of the key differentiating factors about the North American diet is that it is high in refined carbohydrates and sugar and low in antioxidant rich foods such as fruits and vegetables. A number of recent papers have solidified the deleterious effects of sugar in promoting diabetes, obesity, and ultimately cardiovascular disease. In 2010, Jakobsen and colleagues showed that replacing saturated fat with carbohydrates further increased the risk of heart attacks while vegetables had a protective effect. Recent evidence suggests that CAC is driven by insulin resistance. One of the key factors in the development of insulin resistance is a diet high in refined sugars and carbohydrates. Other factors such as hypertension, stress, depression and sleep apnea have also been linked to increased CAC.13

It is clear that it is time to shift our traditional approaches to preventing and managing cardiovascular disease. There is still merit to lowering cholesterol levels in those with a history of a cardiac event, but for most people the primary focus should not be on lowering cholesterol. Interventions that show promise for vascular health are maintaining adequate vitamin D, vitamin K and magnesium levels. The new cardiovascular health approach should emphasize a diet high in antioxidants and fibre, daily physical activity, reducing inflammation, managing stress and maintaining adequate levels of micronutrients, vitamins and essential fatty acids.14

References


Additional References

The Mitochondrial Theory of Aging

The mitochondrial theory of aging (MTA) and the free-radical theory of aging (FRTA) are closely related, and were in fact proposed by the same researcher about 20 years apart. Both theories suggest that free-radicals damage DNA over time, causing one to age, while the MTA just adds the mitochondria and its production of free radicals into the equation. These theories and the understanding we now have of free radicals are the reason that antioxidants are such popular supplements and topics of discussion today.

The Paradox

Mitochondria are like little cells within our cells (see Figure 1 on pg. 22). They are the energy producing organelles of the body. The more energy a certain tissue requires such as the brain and the heart, the more mitochondria those cells contain. What makes mitochondria interesting is that they have their own set of DNA. What makes them paradoxical is that the more energy they produce, the more DNA-damaging free radicals they produce! Mitochondrial DNA damage appears to be caused by the natural by-products of energy or ATP production, meaning that the very process that is meant to sustain life is what eventually causes the dysfunction and death of the cell! Mitochondria may well hold the key to function and dysfunction, and ultimately to life and death!

Think of it this way: all cells, tissues and thus body parts require ATP, or energy, to function properly. If DNA holds the blueprint for the proper function of a cell, then any change in the blueprint will change how the cell functions. If the mitochondria do not function properly, then they cannot fulfill their role in producing energy, meaning that the cell will lose its ability to function adequately.

Many Mechanisms

Dysfunctions of the mitochondria have been proposed in the development of a whole host of degenerative diseases, including diabetes, high blood pressure, Alzheimer’s disease, neurodegeneration and cancer. Researchers have mostly focused on those related to the heart and the brain because they require large amounts of oxygen and energy and are so dense in mitochondria, meaning that mitochondrial dysfunction has a huge impact on the functioning of these organs.

What We Currently Know

Diabetes, Endothelial Dysfunction, Blood Pressure & Reduced Nitric Oxide

In diabetes, high blood sugar and high blood lipids that have been oxidized or glycated impair the function of the mitochondrial enzymes which results in an overproduction of free radicals. These free radicals damage the mitochondrial DNA, make the mitochondria dysfunctional and alter various pathways in the endothelial cells that initiate atherosclerosis and cardiomyopathy (heart muscle disease). They also reduce the activity of Nitric Oxide Synthase in endothelial cells, which reduces nitric oxide production and endothelial-dependent vasodilation, resulting in high blood pressure. This effect has been shown in the arterioles of subjects with type 2 diabetes versus controls without the disease. In those with diabetes, endothelial function was impaired, mitochondrial density was lower, flow – mediated dilation (a measure of blood vessel responsiveness to blood pressure) was lower, and mitochondrial superoxide (a free radical) production was higher.

Toxic Fat!

Mitochondria are also involved in lipid metabolism. If the mitochondria are dysfunctional, then lipid metabolism becomes imbalanced. It is suggested that this dysfunctional partnership may complicate type 1 diabetes through mitochondrial dysfunction in the pancreatic beta cells that produce insulin, disrupting the metabolism of fats and sugars. In type 2 diabetes, it is thought that mitochondrial dysfunction also occurs in fat cells, inhibiting the proper metabolism of fats. This allows excess fats to circulate and be taken up by other cells such as those pancreatic beta cells, resulting in lipotoxicity (fat toxicity) and perpetuating the mitochondrial dysfunction. In humans, a high-fat diet has been shown to increase mitochondrial production of free radicals in muscles, and that when
free radical production was limited with a targeted drug, insulin sensitivity was preserved. Calcium Regulation
Dysfunctional mitochondria are also a hallmark of heart muscle remodeling in disease. It is now thought that mitochondria help regulate calcium flux in the heart cells, helping to regulate its function. Calcium is required for the contraction of muscles, including the heart. If the mitochondria are dysfunctional, their ability to buffer calcium as well as supply energy to the heart are greatly compromised.

Potential Treatment Options Under Study
Exercise for Endothelial and Mitochondrial Dysfunction
It is known that exercise can actually stimulate the multiplication of mitochondria in muscle tissue. This makes sense because if the muscles require more energy, the body will need to make sure the machinery to make that extra energy is available. We also know that exercise improves endothelial function. One study found that in patients with coronary artery disease (CAD), 33% of them had mitochondrial dysfunction. Those 33% tended to have lower physical activity levels, which was associated with greater endothelial dysfunction. The reverse was also true. This shows that lower physical activity levels are associated with greater mitochondrial dysfunction and endothelial dysfunction in CAD patients, that more physical activity could actually reduce both mitochondrial and endothelial dysfunction, and that both types of dysfunction could be related!

Nutritional Support for the Mitochondria
1. Lipoic Acid & Acetyl-L-Carnitine
Calcification of the blood vessels is an important concern today because it leads to hardening of the arteries. Alpha lipoic acid is known to be a mitochondrial antioxidant that preserves or improves mitochondrial function. However, it has now also been shown in vitro and in an animal study that lipoic acid can prevent arterial calcification, and that arterial calcification may even be related to mitochondrial dysfunction! Since lipoic acid is so important for mitochondrial health, methods are under study to increase lipoic acid synthase production, the enzyme responsible for making lipoic acid in the body. A human study on CAD patients has given further proof of the relationship between endothelial dysfunction, mitochondrial dysfunction and heart disease. CAD patients were given lipoic acid and acetyl-L-carnitine for 8 weeks and then a placebo for 8 weeks. L-Carnitine helps shuttle fatty acids into the mitochondria in order to make energy. The treatment was found to relax the blood vessels in all patients. In patients with higher blood pressure and in those with metabolic syndrome, blood pressure decreased by 9mmHg! This shows that treating mitochondrial dysfunction can improve blood vessel function and therefore blood pressure. This is indeed a novel approach!

2. Co-Enzyme Q10
CoQ10 is perhaps the most popular mitochondrial enzyme and antioxidant. It is already well known that statin drugs taken for high cholesterol severely reduce CoQ10 levels, which ironically...
causes other negative cardiovascular side effects. However, a human study on CAD patients has now shown that over 8 weeks of supplementing with 300mg of CoQ10 reversed mitochondrial dysfunction (as measured by a reduced lactate:pyruvate ratio) and improved endothelial function (as measured by increased flow-mediated dilation).14

3. Other Mitochondrial Antioxidants

Other natural compounds that have been shown to have antioxidant effects in the mitochondria include resveratrol, found in wine and grapes, curcumin from turmeric and EGCG, found abundantly in green tea extract. However, human studies have not been conducted for these compounds in mitochondrial dysfunction.16,18

A New Name

So recognized is the role of mitochondrial dysfunction in many diseases that a new term has been coined for this phenomenon: bioenergetic dysfunction.15 Bioenergetic dysfunction is now known to be related to a gamut of diseases including diabetes, hypertension, arterial calcification, Alzheimer’s disease, and even autism (see Figure 2).4,16,17 The most recent research is applying current knowledge of bioenergetics dysfunction to cancer treatments including chemotherapies.16

Quality Mitochondria Equals Quality Health

Not only the quantity of mitochondria but the quality of those mitochondria is important for good health. Exercise can increase the number of mitochondria, but the health of those mitochondria must be preserved with targeted mitochondrial antioxidants. Failure to do so can result in mutations to the mitochondrial DNA. The mitochondria need to be functioning adequately enough to destroy damaged or mutated machinery (mitophagy) in order to remain healthy. In fact, this regulated recycling process is essential in order to lengthen one’s lifespan according to the caloric restriction diet (which by the way is the only proven method to lengthen one’s lifespan and healthspan).15 The bottom line is that all evidence is pointing toward the mitochondria as the key holders to health.

References

A subject that is gaining much attention in many circles of medicine these days is methylation, as it pertains to our body’s functions and in particular the management of homocysteine.

With respect to statistics of heart disease in Canada, according to the Heart and Stroke Foundation, every 7 minutes in Canada someone will die of heart disease or stroke. They are both in the top three causes of death for Canadians. Although numbers have improved with respect to heart disease over the years, these are still very sobering statistics.

Thus, in looking at a preventative approach and management strategy for heart health, the investigation of the process of methylation and specifically homocysteine is an interesting exploration.

Methylation (see Figure 1) is defined as the addition of a methyl group (1 carbon atom bound to 3 hydrogen atoms) to a substrate (molecule upon which enzymes act). This process is used to transport nutrients throughout the body as well as to turn genes on and off. Defaults in methylation have shown to set the stage for assaults from environmental toxins, infectious agents and inflammatory processes, resulting in a wide range of conditions including cardiovascular disease.

### The Importance of the Methylation Pathway

New cell synthesis and repair- defects in methylation can cripple the body’s ability to produce adequate amounts of DNA and RNA. This means that new cell production is impaired and more cells will die than will be created over time. This impairs all aspects of the body as the capacity to heal on any level is reduced.

### Methylation and Heart Disease

Coenzyme Q10 (CoQ10) has been identified as a beneficial molecule for heart health as it feeds the mitochondria within each of our cells. Cardiac tissue is packed with mitochondria, more so than other tissue types in the body. Clinically CoQ10 has been used in the treatment of angina, prevention of heart attack, and protection from reperfusion injury after bypass surgery. The synthesis of CoQ10 in the body relies on components of the methylation cycle, particularly S-adenosyl methionine.

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### Potential Diet and Lifestyle Factors That May Contribute to Elevated Levels of Homocysteine

<table>
<thead>
<tr>
<th>General</th>
<th>Lifestyle factors</th>
<th>Diet</th>
<th>Diseases or Inherited Causes</th>
<th>Drugs that increase Homocysteine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age&lt;br&gt;Male gender&lt;br&gt;Menopause (HRT may lower homocysteine)</td>
<td>Smoking&lt;br&gt;High consumption of coffee&lt;br&gt;Alcohol consumption (moderate beer intake may be beneficial)</td>
<td>Low consumption of fruits and vegetables&lt;br&gt;No consumption of multivitamins&lt;br&gt;Low intake of folic acid, vitamin B6, vitamin B12&lt;br&gt;High intake of methionine-containing proteins</td>
<td>Cystathionine-Synthase deficiency&lt;br&gt;SMTHFR errors&lt;br&gt;Methionine synthase deficiencies&lt;br&gt;Chronic renal failure&lt;br&gt;Diabetes&lt;br&gt;Hypothyroidism&lt;br&gt;Psoriasis&lt;br&gt;Certain malignancies&lt;br&gt;Malabsorption syndrome&lt;br&gt;Rheumatoid arthritis&lt;br&gt;Helicobacter pylori infection</td>
<td>Some antiepileptic drugs (phenobarbital, valproate, phenytoin etc)&lt;br&gt;Diuretic therapy&lt;br&gt;Methotrexate&lt;br&gt;Nitrous oxide&lt;br&gt;Cholestyramine&lt;br&gt;Fibric acid derivatives (fenofobrate)&lt;br&gt;Estrogen-containing oral contraceptives&lt;br&gt;Metformin&lt;br&gt;Niacin&lt;br&gt;Theophylline&lt;br&gt;Sulfasalazine</td>
</tr>
</tbody>
</table>
Poor methylation results in a rise in homocysteine levels and a drop in SAMe levels, thus depleting levels of CoQ10 for proper mitochondrial function within our cells (see Figure 1).

**So What is Homocysteine?**
Homocysteine (see middle of Figure 1) is a sulfur containing amino acid and a normal intermediate of methionine metabolism in the methylation cycle. When excess homocysteine is produced and not converted to cysteine (downstream) or back into methionine (upstream), it is excreted out of the cells and into the blood. It is the role of the liver and kidneys to deal with these excess levels, if and when they do occur. Issues with genetic conditions, diseases of the liver or kidneys, nutrient deficiencies or the use of certain pharmaceuticals can cause elevations in homocysteine to be mismanaged and this can lead to adverse health concerns.

The role of elevated homocysteine levels in clinical practice has been hotly debated; the central theme being whether or not it is beneficial to measure and treat elevated levels of homocysteine. Some may consider homocysteine simply a marker but not a causative agent, while others ignore it as a coincidental metabolite, scientific evidence suggests otherwise.1,2

From a historical perspective, as early as the 1960s, researchers described several inborn errors of metabolism in children which led to extremely high levels of homocysteine in the blood, resulting in mental retardation and death, often the result of a cardiac event. Post mortem examination of these patients revealed an emerging pattern of atherosclerosis due to formation of fibrous plaques and a loss of vascular elasticity. It was concluded by the researchers that these high levels of homocysteine were a directly responsible for these vascular lesions and set the stage for the cardiac events and death.

Homocysteine can be measured with a conventional blood test, albeit important to follow the proper directions for collection so as to ensure consistent homocysteine measurements. Average fasting total homocysteine for “healthy” subjects is considered to be in the range of 6 to 12 umol/L. That being said, many proponents of preventative medicine like to see patients in the lower ranges as close to 6umol/L as possible. Figure 2. displays a graph showing the relationship of odds ratios for coronary artery disease (CAD) increasing with increasing levels of homocysteine in the blood. You can see an almost linear fashion of increased risk between the levels of 6 and 20 umol/L of homocysteine in the blood.

**Risk Factor Assessment**
In a prospective cohort study following 2127 men and 2639 women over four years, increasing levels of plasma homocysteine were directly correlated with increasing mortality (3). The authors concluded at the end of the study, based on their findings, an increase of 5umol/L of homocysteine would increase the all cause mortality by 49%, cardiovascular mortality by 50%, cancer mortality by 26%, and non cancer, non cardiovascular mortality by 104%.

**Possible Mechanisms Associated With High Levels of Homocysteine**
- Oxidative damage – much of the endothelial dysfunction associated with high homocysteine is thought to be from oxidative stress.4,5
- Nitric oxide – studies have shown that homocysteine suppresses the vasodilator nitric oxide contributing to decreased vascular endothelial compliance and changes in platelet coagulation (6-10)
- Vascular smooth muscle proliferation – studies have shown homocysteine’s ability to trigger proliferation of vascular smooth muscle cells thereby decreasing the lumen size of the vessel (11-15)
- Endothelial cell cytotoxicity - high levels of homocysteine have been shown to be a contributor towards this issue, causing the formation of vascular lesions within the cardiovascular system and beyond (13)
Homocysteine lowering ideas

- Folic acid – while lower doses of folic acid have been shown to be effective in reducing homocysteine in the general population, those with cardiovascular concerns require much higher levels to be therapeutic, 2-15 mg/day have been used.\textsuperscript{16-18} It should be noted that at these higher folate levels, vitamin B12 be given in conjunction, to prevent any masked B12 deficiencies.
- Vitamin B12 – vitamin B12 deficiency can be common with vegetarians and the elderly, and is often detected with a finding of elevated homocysteine.\textsuperscript{19}
- Vitamin B6 – usually given in conjunction with the above 2 vitamins, B6 shows much less benefit as a monotherapy.
- TMG – trimethyl glycine – using TMG to remethylate homocysteine, this nutrient has shown promise as well in lowering elevated homocysteine levels.
- Combination product (MaxMethyl from AOR) – has been shown to significantly reduce homocysteine levels after just 6 weeks of supplementation.

**Summary**

Proper methylation is an important process that occurs within our bodies. Homocysteine is a valuable marker to follow with respect to management of heart health both from a preventative aspect but also to monitor it when dealing with cardiovascular disease or in a post surgical protocol. It is important to realize the significant benefit of vitamins like folic acid, B12 an B6 and products like MaxMethyl from AOR as effective strategies for reducing the body’s level of homocysteine if it is shown to be elevated. It is also valuable to utilize these nutrients to promote the proper function of the methylation cycle as a key to long term wellness.

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**References**


**Additional References:**

http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.3581729/k.359A/Statistics.htm
http://www.nature.com/cdd/journal/v11/n1s/images/4401451f1.jpg
The following table is intended to give a general overview of AOR’s Heart formulas and the main areas of cardiovascular health targeted by each product.

<table>
<thead>
<tr>
<th>AOR Product</th>
<th>Type of Product</th>
<th>Main Cardiovascular Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall Heart Health</td>
</tr>
<tr>
<td>Advanced Cardiac Support</td>
<td>AOR’s top nutrient blend for overall heart health featuring Powergrape’</td>
<td>***</td>
</tr>
<tr>
<td>Arjuna Flow</td>
<td>Ayurvedic herb</td>
<td>**</td>
</tr>
<tr>
<td>Cardana Caps</td>
<td>AOR’s top Ayurvedic herbal blend for heart health</td>
<td>***</td>
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<tr>
<td>Cardio Mag 2.0</td>
<td>AOR’s top magnesium: fully chelated magnesium orotate</td>
<td>***</td>
</tr>
<tr>
<td>CardioNOx</td>
<td>The NOx line best-seller: CoQ10 and nitric oxide</td>
<td>***</td>
</tr>
<tr>
<td>CoQ Plus / Co-Enzyme Q10</td>
<td>Vital nutrient and antioxidant</td>
<td>**</td>
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<tr>
<td>Chromium Picolinate</td>
<td>Trace mineral</td>
<td></td>
</tr>
<tr>
<td>De Cholest</td>
<td>AOR’s top herbal blend for cholesterol</td>
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</tr>
<tr>
<td>Garlic Alkalized</td>
<td>Patented, alkalized, non-odorous garlic formula</td>
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<tr>
<td>Gymnema-75</td>
<td>Ayurvedic herb</td>
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</tr>
<tr>
<td>Hawthorn II</td>
<td>Popular and powerful herb</td>
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</tr>
<tr>
<td>Mag K Taurine</td>
<td>Electrolyte and amino acid formula</td>
<td>**</td>
</tr>
<tr>
<td>Mag Taurate</td>
<td>Mineral and amino acid formula</td>
<td>**</td>
</tr>
<tr>
<td>MaxMethyl</td>
<td>AOR’s top methylation &amp; homocysteine blend</td>
<td>***</td>
</tr>
<tr>
<td>Mecofolate</td>
<td>High-dose active B6 and B12 combo</td>
<td>**</td>
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<tr>
<td>Niacin No-Flush</td>
<td>Non-flushing vitamin B3</td>
<td>*</td>
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<tr>
<td>Opti-Guggul II</td>
<td>One of Ayurveda’s most prized multitasking herbs</td>
<td></td>
</tr>
<tr>
<td>Ortho Glucose II</td>
<td>AOR’s top herbal, mineral &amp; nutrient blend for blood sugar balance</td>
<td>***</td>
</tr>
<tr>
<td>Ortho Heart</td>
<td>AOR’s top herbal, vitamin &amp; mineral blend for blood pressure balance</td>
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</tr>
<tr>
<td>Pantethine</td>
<td>Active Vitamin B5</td>
<td></td>
</tr>
<tr>
<td>Pronogenol-2</td>
<td>Capitalize on the best benefits of grapes</td>
<td>**</td>
</tr>
<tr>
<td>Stamina Shot</td>
<td>Magnesium, beetroot juice &amp; nitric oxide in a liquid shot</td>
<td>**</td>
</tr>
<tr>
<td>Total E</td>
<td>Naturally extracted full vitamin E spectrum of 4 tocopherols and 4 tocotrienols</td>
<td>*</td>
</tr>
<tr>
<td>TLC 3.0</td>
<td>AOR’s favourite arterial health formula with high-dose Vitamin C, amino acids &amp; electrolytes</td>
<td>***</td>
</tr>
<tr>
<td>VeinEase</td>
<td>AOR’s top herbal blend for healthy veins</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin C with Beets ‘n’ Berries</td>
<td>Blend of fruit, veggie &amp; grass powders to maintain good health</td>
<td>***</td>
</tr>
</tbody>
</table>

*** strong evidence, multiple modes of action
** moderate evidence
* some evidence, single mode of action
CARDIONOX

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Co-enzyme Q10 enhanced with a natural source of supplemental nitric oxide

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