Synergy in Nutrients

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Natural medicine had its beginnings in the use of whole foods at the outset of human history. Prior to the advent of modern encapsulated natural medicine, our ancestors utilized medicines in their natural states without improvements (other than by increasing supply and storage). A central tenet of natural medicine is that food is medicine.

Nature's bounty is shown to be truly amazing when we consider the diverse array of natural medicines (and nearly 35 percent of pharmacologic medicines) that are derived from mainly plants and minerals. Hippocrates' age-old wisdom stated: "Let your food be your medicine and let your medicine be your food." This adage eloquently highlights this principle.

The majority of humans who have ever lived on this planet (and those living today) overwhelmingly utilized natural medicines. The use of modern (conventional) medicines (as defined by substances other than foods) began roughly 150–200 years ago.

Advances in medical technology have even led us away from the whole-food approach toward a pharmaceutical mentality, as whole medicines are continually separated into increasingly individualized "active" components and placed into pills. Despite these technological advances in the process of identification and isolation of active components, we are seeing that this process does not entirely guarantee the ultimate use of a whole medicine. Humankind never matches the mastery of whole-food medicines in quite the way nature has assembled them for us.

Today, close to one third of Americans alone use some form of nutritional medicine currently. This is an optimal situation because processed foods and synthetic drugs take their toll on health. It is both amazing and not surprising that, in order to maintain normal physiologic functioning, we are dependent on whole-food–derived supplements. Because of this, our choices in utilizing and understanding nature's pharmacy dictate how we use this bounty from which humans have benefited throughout time.

Coenzyme Q10

Found in high concentrations in the heart muscle and other highly metabolic organs (the brain and liver), coenzyme Q10's (CoQ10's) main purpose appears to be to serve as a cofactor in energy-producing pathways. Perhaps the most important function is the synthesis of adenosine triphosphate (ATP), the body's currency of energy during oxidative respiration.[1] CoQ10 is found in increasingly higher concentrations within cells, with the highest amounts found in the mitochondria, where all cellular energy is produced. Other important functions of CoQ10 include antioxidative and cellular membrane stabilization.[2]

CoQ10 works in the final step in energy production (ATP synthesis) and can also prevent metabolically induced damage (via antioxidant and membrane stabilization) to the cardiovascular system. Not only useful in the cardiovascular system, CoQ10 can be used to treat diseases of the muscle, connective tissues, and brain, among others.

L-Carnitine

The amino acid L-carnitine is synthesized from two other amino acids, lysine and methionine, and 98 percent of L-carnitine is found in heart tissue and skeletal muscles. L-Carnitine is vital for heart-tissue health because this amino acid plays an essential role in transporting free fatty acids into the mitochondria, where they undergo beta-oxidation, a source of energy production in the heart.[3]

Low levels of L-carnitine have been observed in patients suffering from angina pectoris. Using a supplement with L-carnitine can reduce the number of angina episodes, increase exercise performance, and reduce ST segment depression (a marker of cardiac-muscle oxygen starvation on an electrocardiogram).[4]

Levels of L-carnitine are reduced in up to 50 percent in diseased hearts,[5] and use of this supplement can reduce symptoms of congestive heart failure and increase survival.[6] Heart diseases, such as ischemic cardiomyopathy, heart failure, hypertrophy, and dilated cardiomyopathy, all have a similar problem in energy metabolism: ATP synthesis is decreased because inadequate fatty-acid fuels are delivered to the mitochondria. L-carnitine has been indicated as a key nutrient that is depleted in these diseases.[7] Similar to coQ10, L-carnitine is a key nutrient in heart-muscle metabolism and energy production.

CoQ10 and L-Carnitine

CoQ10 and L-carnitine assist mitochondrial energy production and prevent oxidative damage in the heart.[8] Taken together, these nutrients assist the heart muscle by increasing transport of crude energy sources (fatty acids) into the mitochondria whereupon beta-oxidation yields energy for the working tissue. When the breakdown of fatty acids is complete, ATP is produced, the body's self-created energy source. CoQ10 is needed in this process for final synthesis of energy for the heart. The protective

effects of these nutrients, when used in combination, have been demonstrated in laboratory animals that were subjected to reperfusion injuries.[9]

Investigators demonstrated that, when used in association with each other, these compounds were more effective for preventing oxidative damage and metabolic abnormalities (hemodynamic parameters) than when used individually.

In addition to their role in cardiovascular health, CoQ10 and L-carnitine, with the abovementioned mitochondrial energy production and antoxidative capabilities, may play a role in the prevention and treatment of Parkinson's disease.[10] Strong evidence suggests that mitochondrial dysfunction and concomitant oxidative damage are integral in the pathogenesis of this disease and further study of the protective effects of these nutrients are needed. Evidence from animal studies suggests that these nutrients may indeed be helpful.

L-Carnitine can play a role in addressing reperfusion injury when used with CoQ10.

Another condition in mitochondrial dysfunction plays a role is age-related macular degeneration (ARMD). Researchers who observed the utility of nutritional compounds for improving mitochondrial functions (mitotropic compounds) tested L-carnitine and CoQ10 among others (polyunsaturated fatty acids and vitamin E).[11] Patients with ARMD were treated with a mixture of mitotropic compounds.

Measures of macular acuity (recovery time following photostress, foveal sensitivity, and mean visual-field defects) were measured and compared in subjects who took the mixture to these parameters in patients who were given only vitamin E. Follow-ups over the next 3, 6, 9, 12, and 24 months revealed improved visual functions in all areas and improvements remained stationary throughout the follow-up period while the patients in the control group experienced worsened symptoms. The literature describes several other instances of synergistic benefits from using these nutrients together.

Choline

Recently, it has been discovered that choline, long considered to be a B vitamin, is produced in very small amounts in the human body. Although produced endogenously, the amount of choline is quite minimal and, when it is taken in supplemental doses, has several beneficial effects in the body. Produced in the liver, choline is used to synthesize cellular membranes[12] and works as a methyl donor to create new compounds in the body. This process is important in the creation of DNA and in the conversion of homocysteine (an amino acid with negative effects on the cardiovascular system) to methionine.

Choline, in the form of phosphatidylcholine, can increase the solubility of cholesterol in the body, lower cholesterol levels, and inhibit platelet aggregation.[13] In a study, 32 patients with elevated cholesterol and triglycerides were treated with 3.5 g of phosphatidylcholine 3 times per day before meals. Among the subjects, cholesterol levels decreased by 33 percent, triglycerides by 33 percent, and high-density lipoprotein cholesterol increased by 46 percent after 30 days of treatment.[14] In supplemental form, choline is useful for accelerating the metabolism of cholesterol and in energy production.

Choline and L-Carnitine

When supplemented with L-carnitine, choline decreases urinary excretion and renal clearance of L-carnitine. In one study, subjects treated with choline had decreased urinary L-carnitine clearance by up to 84 percent.[15] In another study, young adult women that took choline at 20 mg per kg of body weight had a 75-percent lower urinary L-carnitine excretion than a control group, and plasma L-carnitine levels were not significantly altered.[16] A combination of both nutrients can be beneficial for retaining L-carnitine, allowing for greater metabolic utilization of this nutrient.

L-Carnitine and Vitamin C

Vitamin C, or ascorbate, acts as a cofactor in the synthesis of L-carnitine, specifically in two alpha-ketoglutarate–requiring dioxygenase reactions in the pathway of L-carnitine biosynthesis.[17] Investigations have revealed that higher supplemental amounts of ascorbate will enhance L-carnitine synthesis.[18] Results from a study of ascorbate and L-carnitine biosynthesis showed that increased concentrations of supplemental ascorbate resulted in enhanced ketogenesis and decreased triglyceride accumulation, suggesting that L-carnitine synthesis is dependent on ascorbate.[19]

As mentioned earlier, L-carnitine can play a role in addressing reperfusion injury when used with CoQ10. Additional evidence cites the importance of vitamin C and L-carnitine for treating reperfusion injury.[20] In laboratory animals, ischemic changes were seen less frequently in tissue samples treated with both vitamin C and L-carnitine compared to tissue samples obtained from control and placebo groups. The researchers concluded that these nutrients are effective for reducing reperfusion injury in skeletal muscle.

Another example of the synergistic uses of L-carnitine and ascorbic acid lies in their relative amounts in the body. In order to determine if L-carnitine metabolism is a useful parameter for determining vitamin C requirements, researchers investigated whether a diet with controlled amounts of vitamin C would affect L-carnitine levels.[21]

Plasma levels of free L-carnitine (and histamine, another study parameter) were inversely related to vitamin C status. This indicates that L-carnitine levels are altered in subjects with subnormal, but nonscorbutic vitamin C status, indicating that metabolic changes other than collagen metabolism dysfunction occur before scurvy becomes manifested.

Therefore, researchers suggest that using the appearance of scurvy as an endpoint in determining vitamin C requirements may not be useful in establishing reference amounts of vitamin C for optimal health status. Because of the necessity of vitamin C in the synthesis of L-carnitine, and the energy producing effects of L-carnitine, vitamin C should be supplemented with this amino acid to ensure proper function and optimal energy production.

Flavonoids

Flavonoids are a large grouping of plant pigments responsible for the darker coloring of various fruits, vegetables, and other plants. These phytoestrogens are well-known for their affinity for the vascular system and the supportive role they play in decreasing capillary fragility, preventing breakdown of venous support structures, and increasing the tone of the muscles surrounding certain parts of the vasculature.[22]

Flavonoids have been well-studied in relation to vasculature disease. Research has shown decreased postinfarct tissue damage, decreased incidence of ventricular fibrillation, decreased free radicals in heart muscle fluids, improved postmyocardial-infarct ventricular function, and reduced amounts of foam cells (an early manifestation of atherosclerosis) all following supplementation with flavonoids.[23]

Magnesium, in addition to its use in preventing heart diseases, is necessary for absorption of vitamin B_6.

Phytoestrogen supplementation can also decrease the amount of oxidized low-density lipoprotein (LDL) in patients with elevated blood cholesterol, as demonstrated in the abovementioned studies. Flavonoids derived from grape (*Vitis vinifera*) seed extract decrease the activity of proteolytic enzymes that are responsible for breakdown of connective tissues, thereby preventing premature destruction of venous structures.[24]

Flavonoids derived from bilberry (*Vaccinium myrtillus*) have strengthened and stabilized collagen synthesis,[25] as well as decreasing vascular permeability and fragility, thereby preventing capillary leakage and swelling.[26] When used to treat cholesterol-induced atheroma, bilberry flavonoids decreased pathologic proliferation in blood vessel linings, lipid deposition, and calcium deposition in the lesions.[27]

Flavonoids and Vitamin C

When combined with vitamin C, flavonoids will enhance the vitamin's function by improving its absorption and protecting it from oxidation in the body. One study revealed that, when administered in combination with a flavonoid-rich citrus extract, ascorbate was absorbed by an increased 35 percent over ascorbate that was administered alone.[28]

Another investigation demonstrated the antioxidative abilities of soy (*Glycine soja*) and alfalfa (*Medicago sativa*) extracts, both of which have flavonoids as main active ingredients.[29] The two extracts had notable antioxidant capability as expressed by decreased LDL oxidation; however, when acerola cherry (*Malpighia glabra*) extract (which is rich in ascorbic acid) was added, the antioxidative effect was enhanced further.

The investigators concluded that ascorbate could enhance the activity of flavonoid-rich antioxidants. It was suggested that that this synergistic activity was the result of the "peroxidolitic" action of ascorbic acid complemented by flavonoid-induced stabilization of the LDL in this particular study and the suppression of free-radical species propagation. This research team also noted that the combination decreased the amounts of phytoestrogens needed to achieve significant antioxidative activity.

These studies demonstrate the protective mechanism by which bioflavonoids help to stabilize and strengthen the vasculature as well as preventing cardiovascular disease processes.

Magnesium

Inadequate intake of magnesium is associated with the development of cardiovascular diseases, including hypertension, cardiomyopathy, atherosclerosis, and strokes.[30] In addition, suboptimal tissue stores are implicated in increased heart arrhythmia and cardiovascular-disease complications.[31] Population studies associate higher circulating blood levels of magnesium with decreased risks of coronary heart disease[32]; imbalances of intracellular levels of minerals such as magnesium are associated with cardiovascular disease.[33]

Adequate magnesium intake is consistently associated with healthier heart statistics, most probably the result of this mineral's effect on lowering blood pressure. Keeping blood pressure low is an integral part of heart-disease prevention because hypertension is often a reliable predictor of heart disease in later life.

Magnesium and B Vitamins

Magnesium, in addition to its use in preventing heart diseases, is necessary for absorption of vitamin B_6. Investigators have revealed that a deficiency of magnesium will impair vitamin B_6 status via a decreased ability of intracellular magnesium to stimulate alkaline phosphatase, an enzyme that is required for uptake of pyridoxal phosphate in tissues.[34]

One study demonstrated the ability of high serum homocysteine levels to deplete magnesium levels in cerebral vascular smooth-muscle cells (VSMCs).[35] Depletion of magnesium was not prevented by incubating the VSMCs with vitamin B_6, folic acid, or vitamin B_{12} alone. When investigators combined all three vitamins however, the loss of magnesium was completely inhibited.

These findings are further evidence to support the hypothesis that elevated homocysteine serum levels lead to abnormal metabolism of magnesium in cerebral VSMCs, thereby priming the cells for homocysteine-induced atherogenesis, vasospasms, and stroke. This study demonstrated a need for all three vitamins

in addition to adequate magnesium (to achieve physiologic levels) to prevent cerebral vascular diseases that are induced by homocysteinemia.

Conclusions

Upon hearing the amazement in a person's voice as he or she expresses a newfound improvement in health after merely changing a diet, it is a reminder of the how truly amazing and efficiently the human body responds to the addition of relatively simple nutritional strategies as well as these effects on the physical and mental realms.

Despite our many medical technological advances, medicine is far from achieving the ability to mimic natural medicines in their native states. Remembering (and continually discovering) the many ways in which simple nutritional factors work in the body, and that, rarely, does one nutrient achieve what many working in combination will, positive improvements can be made in the direction of true healing.

Remembering that nature's wisdom is responsible for the synergism of its bounty, practitioners of natural medicine must remember how powerful the sum of these nutrients is when using nutritionally based medicines. □

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