SOME Drug / Nutrition Interactions of Interest

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This paper is not intended to be a complete review and it is presented here mostly without references. [Note: all the information is derived from the legitimate scientific literature and not from goofy things on the internet.] It is intended to be just a closer look at a collection of medication/nutrition interactions that have been especially problematic for my patients, and some suggestions for minimizing problems. There are (of course) many other drug/nutrition interactions that are not covered here and that I don't know a thing about. ☺. Drug/Drug interactions are also not included here. As always, it is not intended to take the place of advice from your health care provider.

Anti-Seizure/Epilepsy Medications

<u>All</u> seizure medications cause <u>vitamin D</u> to turn over faster.

For that reason, the intake needed to maintain healthy blood levels of vitamin D are higher than usual. **Vitamin D inadequacy is common in the general population, and it is especially prevalent among people taking seizure-control medications.**

Vitamin D deficiency is associated with many health problems, including increased risk of cancer, congestive heart failure, impaired immune function, depression, muscle weakness, osteoporosis, falls, pain, and increased risk of all autoimmune disorders, such as Type I diabetes, MS, arthritis, lupus and more. RDA/RDI/AI levels at the moment are not associated with optimal vitamin D levels even among healthy people, and they are very unlikely to assure adequacy among people using these medications.

Recommended in general:

Maintain a vitamin D blood level at about 40-50 mg/dL. In certain cases (e.g. cancer patients,) 60 mg/dL or more is often a preferred goal.

Ideally, get a blood level to determine current status. The blood test is called a "25(OH) vitamin D level." Then give a therapeutic dose of vitamin D to correct it if the level is low. (Many places do this using a dosage of 50,000 iu vitamin D/week x 8 weeks, followed by a re-check; sometimes this has to be repeated.) Then provide an intake level sufficient to maintain the 40-50 range (which may be found to require supplementation to provide 2000-5000 iu/day.) For more on this topic please see "My Current Top Five Easy Ways to Improve Your Family's Nutrition (subject to change at any moment!") "Vitamin D: A Quick Review of Forms, Labs and Other Things People Have Asked Me About Recently." Thoughts about Nutrition and Breast Cancer Prevention

All seizure medications cause decreased absorption of a B-vitamin called biotin.

Biotin (vitamin B7) is involved in many metabolic pathways, including the TCA Cycle to make ATP (making usable energy from food), and gluconeogenesis (making glucose out of amino acids.) Deficiency in general seems to be uncommon in healthy people, but when it does occur it has been known to result in a number of serious problems. It has been shown to contribute to depression, hallucinations, increased infections, poor muscle control, loss of hair, skin problems, seizures and developmental delay in infants.

Eggs, nuts and legumes like peanuts are among the very best dietary sources. Eggs do contain a protein called avidin that makes biotin be poorly absorbed if the egg is eaten raw, but cooked eggs are excellent sources of biotin … and they are also safer to eat in terms of food-borne illness risk. The yolk has most of the biotin.

The intake of biotin that is assumed to meet the needs of most healthy people is about 30 mcg/day. In addition to all seizure medications, alcohol also impairs absorption of biotin. Additionally, chronic antibiotic use decreases the biotin usually produced by bacterial activity in the large intestine. People with intestinal absorption problems (such as inflammatory bowel disease or poorly controlled celiac disease) have also been observed to become deficient in biotin. It also appears that biotin supplementation can be useful for people with diabetes in particular. For more on this topic please see "Thinking about OTHER Nutrition Issues in Diabetes."

Because a very high biotin intake has no known detrimental effects, supplementation above levels recommended for healthy people is very reasonable for anyone on chronic seizure medications or in other situations described above. The normal daily recommended intake for biotin is 30-100 mcg/day. Not all multivitamins even contain 30 mcg biotin. However, it is easy to provide it singly if desired. For example, there are over-the-counter biotin supplements that provide 600 mcg, and it can also be found in variable amounts as a part of "B-complex" vitamin supplements.

Some Specific Seizure Medications That Interact with Nutrients.

In addition to the vitamin D and biotin interactions associated with ALL seizure medications, there are some specific additional interactions with certain medications.

Phenytoin (Dilantin)

Folic acid deficiency is associated with use of this medication if appropriate supplementation is not provided. However, there are some safety issues to consider: When starting the prescription for phenytoin, it is recommended that people start folic acid supplementation right away. If a person is already on the drug and found to be folic acid deficient, generous and rapid folic acid supplementation can cause problems.

In the latter case, the physician can introduce supplemental folic acid slowly to avoid breakthrough seizures, and to work up to achieving a normal blood folic acid level. This is important because it is clearly not safe to simply let the person remain folic acid deficient.
Folic acid deficiency is associated with birth defects, poor DNA production, depression, high homocysteine level, increased risk of stroke and cardiovascular disease, and impaired immune function.

The 1998 introduction of fortification of grain products with a well-absorbed form of folic acid in the US improves the odds of preventing some of the folic-acid related problems in the US today. However, requirements continue to be higher than for people not using phenytoin. The usual intake suggested for most healthy people is 400 mcg folic acid /day, with at least 600 mcg recommended in pregnancy. "Prenatal vitamins" often have 800 mcg of folic acid, but they often do not contain many other nutrients. For that reason, just recommending a prenatal vitamin is often not a good solution to this problem.

A better approach would be to provide as complete a regular multivitamin with minerals daily as possible, and add one or more tiny 400 mcg folic acid tablets. Food sources include leafy greens and orange juice, but it is not clear that folates in the form found naturally in foods are as well absorbed as supplemental forms among people using this medication. And, as it is well known that there is significant genetic variation in one's ability to obtain folic acid from non-supplemented food sources, **it is very reasonable to be generous.**

Folic acid supplementation is simple, easy, cheap and safe at intake levels of more than 1000 mcg/day from supplements and fortified foods. That "upper limit" is based on the old concern that there was a possibility that higher amounts might "mask" vitamin B12 deficiency, as recognized by elevated blood cell size. **It was not due to any observed toxicity of the vitamin.** However, having large red blood cell size (Mean Cell Volume on a laboratory test) is a **very late appearing symptom of vitamin B12 deficiency** and it is no longer to be relied upon to detect deficiency. There are much more useful measurements easily available today. **Therefore, there is no vitamin B12-related reason to limit intake of folic acid.**

Instead, steps described later should be able to prevent vitamin B12 deficiency, so the "masking deficiency of vitamin B12" concern is no longer an issue. There is also no evidence that naturally occurring folates in foods pose any threat to health. For more on this issue please see my paper: "Vitamin B12.")

In view of the well documented effect of phenytoin on folic acid status, it is reasonable to monitor this, e.g. via erythrocyte folate levels, to determine the amount of supplementation needed by an individual already on the drug. Before starting phenytoin, and in the absence of the ability to monitor the situation with laboratory assessment, it is reasonable to just begin a generous intake and maintain it … e.g. a regular intake of 1000 mcg supplement daily.

This amount can be provided in a tiny pill by prescription and over-the-counter. Levels of supplementation well above that have long been available over-the-counter in Europe and elsewhere because of the excellent safety profile. One could also achieve an intake level around that amount (1200) in the USA from, for example, taking a standard multivitamin plus two tiny 400 mcg folic acid tablets without prescription.

The use of this medication is associated with birth defects and a Fetal Phenytoin Syndrome has been described. Relative inadequacy of many B vitamins (including folic acid) induced by use of this medication appears to contribute to the degree of damage. For this reason, optimizing nutrition status in women of childbearing age is especially important. But really … it is mighty important for everyone. [Please see my "Folic Acid Absorption" and "Thinking about Prenatal Nutrition and Fetal Alcohol Syndrome" papers for details.]

Vitamin B12 absorption is also impaired by phenytoin, so monitoring adequacy of vitamin B12 is important. As noted, normal Mean Cell Volume (red blood cell size) is NOT a useful assessment of adequacy … by the time the cells are overly large, a lot of other damage has already occurred, and not all of it is repairable. A serum B12 level would be a much better test if one feels that a test is needed.

[To obtain the most reliable and specific functional measure of vitamin B12 status, one could get a methylmalonic acid (MMA) level, which is more sensitive than a serum vitamin B12 level. However, this is not as available and it is more expensive.]

As vitamin B12 is extremely safe and stored well in the body, one approach would be to give **vitamin B12 shots** at regular intervals (i.e. monthly to yearly, depending on the dosage) which completely bypasses the entire vitamin B12 deficiency risk and it also does not rely on a person taking daily supplements.

Vitamin B12 is affected by other medications as well, and by age and by certain dietary practices. Please see more detail about vitamin B12 in the section below called "Gastro-esophageal reflux (GERD) hyperacidity," and see my "Vitamin B12" paper for further details.

Some Additional Phenytoin B Vitamin Issues:

Thiamin (Vitamin B1) levels in the blood are depleted by the use of phenytoin. Thiamin is critical for energy metabolism, and deficiency can also cause serious neurologic injury.

Riboflavin (Vitamin B2) can also be depleted because the drug increases production of a liver enzyme that destroys it. Supplementation of both B1and B2 is in order.

Vitamin B6 (pyridoxine) is also affected by intake of phenytoin, but there is a special caveat about taking the "B-100 complex" type of supplement: with this particular medication 100 mg vitamin B6 may be too high. Vitamin B6 increases the breakdown rate of phenytoin, so taking relatively high doses (e.g. 50-100 mg) may be a factor in decreased effectiveness of the drug. As described earlier, the "B-100 Complex"-type of supplement would provide 100 mg, so this would not be the best choice in this instance.

However, this does NOT mean that people should be made deficient of vitamin B6. This vitamin is critical for many metabolic functions, including all protein metabolism, energy metabolism, DNA production and nervous system function. The usual recommendation for most folks is 1.5-2.0 mg/day. That

amount should certainly be provided, and people on this drug will very likely need more than that "healthy people" recommended level**. Notice that the levels that were problematic are about 30-50 times the usual recommendation**. If a person requires an extremely generous intake of vitamin B6 for other medical reasons, it might result in needing a different (higher) dose of Dilantin.

Other Vitamin Issues with Certain Seizure Medications:

Vitamin B12 status **can be affected by Primidone (Mysoline.)**

Vitamin B2 (riboflavin) can be depleted by **Phenobarbital** because the drug increases production of a liver enzyme that destroys it. Supplementation is in order.

Carnitine is a substance one's body makes that is needed to use fat for energy.

Carnitine production is impaired by Valproate / Valproic Acid (Depekene) and also by Phenytoin. Carnitine inadequacy increases the liver toxicity of valproate.

Carnitine inadequacy also contributes to very low blood sugar in certain contexts. It also contributes to the side effects of lethargy and excessive weight gain noted with this medication. High triglycerides and poor control of insulin-treated diabetes have also been seen.

Impaired production of carnitine can also lead to "breakthrough seizures" because inadequacy also impairs the utilization of the seizure medication itself. Supplemental carnitine is recommended and it is now easily available by prescription and over-the-counter. (Please see my paper " A Discussion about Carnitine" for specific details.)

Stomach Acid Blockers for Hyperacidity or Gastroesophageal Reflux Disease (GERD)

Proton Pump Inhibitors (PPIs) block production of stomach acid by over 90%. However, the form of vitamin B12 found naturally in foods of animal origin requires stomach acid for absorption.

The crystalline vitamin B12 form found in pills (e.g. multivitamins or just vitamin B12 alone) or in fortified foods bypasses this problem, so supplementation in pill form is strongly advised. Vitamin B12 supplements are very tiny, safe, cheap and easy to use. Sublingual vitamin B12 and B12 injections are also potentially beneficial of course, but these forms are not mandatory if the only absorption issue is lack of stomach acid.

The form of vitamin B12 added to food is also of this crystalline type so loss of stomach acid does not interfere with vitamin B12 absorption from this source. This includes, for example, fortified cereals, infant formulas and vitamin-supplemented beverages.

The amount of vitamin B12 provided in these food forms needs to be considered when determining adequate intake. For example, if one drinks a fortified beverage, what number of ounces would achieve the recommended amount? Eight ounces (1 cup) of some products provide 100%, but many products provide that amount only in about a quart a day. Check the label, or just add additional vitamin B12 via a multivitamin or a separate vitamin B12 pill. Vitamin B12 is extremely non-toxic.

As described earlier related to phenytoin (Dilantin) use, vitamin B12 deficiency is associated with birth defects, poor DNA production, depression, high homocysteine level, increased risk of stroke, and serious neurologic damage. **Deficiency is often missed until significant damage has occurred, in part because common blood tests like Mean Cell Volume (that identify overt deficiency by enlarged cell size) only pick up very late- appearing symptoms**.

[Note that vitamin B12 absorption can be impaired by factors other than absent stomach acid, so the above recommendations related to PPI use will NOT correct other factors that interfere.]

Examples of this kind of 'non-stomach-acid-related" vitamin B12 absorption problems include:

1. **Loss of production of a stomach-produced substance called Intrinsic Factor (IF),** which impairs absorption of vitamin B12 in the intestine. Intrinsic Factor may be inadequate among:

- elderly people because of changes due to stomach atrophy affecting IF production.
- people with a potentially debilitating autoimmune condition called "Pernicious Anemia," that causes inability to produce IF in the stomach.
- people with surgical removal of the stomach (gastrectomy.)
- people who have had certain forms of gastric bypass surgery.

2. **Damage or interference at the terminal ileum (the last part of the small intestine) can also make even generous oral intake of vitamin B12 inadequate.** This is the only location in the GI tract where vitamin B12 can be well absorbed. This includes people with intestinal conditions such as:

- inflammatory bowel disease,
- poorly controlled celiac disease
- "short bowel" due to intestinal surgery
- bacterial overgrowth of the bowel can also impair vitamin B12 absorption.

People with any of these conditions will generally need to obtain vitamin B12 via another route. **Vitamin B12 shots or special sublingual or nasal application forms are needed if the absorption problems above are not resolved.**

As discussed later, this also likely to be needed when the medication **Metformin (Glucophage)** is used. The interference with vitamin B12 absorption in the intestine in this case is caused by a different type of problem, and estimates are that about a third of people using this medication chronically may be vitamin B12 deficient.

Vitamin B12 deficiency takes a long time (e.g. two years) for symptoms to become evident, and the consequences of inadequacy are very serious. So, it is critical that people using PPIS or who have "achlorhydria" (inadequate production of stomach acid for any reason) assure an adequate oral intake of an absorbable form of vitamin B12. Other conditions often require an administration route that bypasses the GI tract, such as injections or sublingual forms.

PPIs can also result in decreased absorption of inorganic iron and zinc due to decreased acidity. Organic forms (like heme-iron and zinc in meat and lactoferrin in mother's milk) are not affected, but plant forms and pill/supplement forms (like ferrous sulfate, etc.) can be significantly less well absorbed.

However, other dietary features can modify this effect in either direction. For example, adding meat to the meal improves absorption due to the presence of "Meat Protein Factor," and the addition of acidic foods (like orange juice and vitamin C) also enhances absorption of inorganic iron and zinc somewhat in this context.

Conversely, substances naturally occurring in certain plant foods, such as phytates (in grains), oxalates (in certain leafy vegetables) and tannins (in tea,) will significantly impair absorption of inorganic iron and zinc. Interestingly, milk consumption also significantly impairs absorption of inorganic iron and zinc. (Please see my "Nutrition Support of Iron Deficiency" paper for more details on this.)

Calcium supplements are also less well absorbed, but a generous intake and --more importantly --assuring a generous vitamin D intake will help prevent problems. Most of the differences in absorption of various forms of calcium are only clinically important in the absence of the normal hormonal regulation by vitamin D. When vitamin D is adequate, the role of relative acidity in calcium absorption is much less important. But it is also true that vitamin D inadequacy is an epidemic in some populations even in the US. For example, the World Health Organization reports that about 50% of the world's population is likely to be vitamin D deficient for many reasons.

Magnesium absorption can also be impaired by these medications, and intake is often suboptimal in the US. Assuring a generous intake is a very good idea. Poor magnesium status increases risk of insulin resistance, osteoporosis and leg cramps. [More on this later … please see my Calcium and Magnesium papers for more detail.

This is fairly newly recognized, so I am including a few references here on

PPI Use and Magnesium Status:

Impact of proton pump inhibitor use on magnesium homoeostasis: a cross-sectional study in a tertiary emergency department. Int J Clin Pract. 2014 Jun 4; Interaction of magnesium oxide with gastric acid secretion inhibitors in clinical pharmacotherapy. Eur J Clin Pharmacol 2014 May 13; The association of proton pump inhibitors and hypomagnesemia in the community setting. J Clin Pharmacol. 2014 Apr 28; Treatment of hypomagnesemia. Am J Kidney Dis. 2014 Apr;63(4):691-5. Contemporary view of the clinical relevance of magnesium homeostasis. Ann Clin Biochem. 2014 Mar;51(Pt 2):179-88. Lansoprazole-induced hypomagnesaemia. BMJ Case Rep. 2014 Jan 10;2014. Out-of-hospital use of proton pump inhibitors and hypomagnesemia at hospital admission: a nested case-control study. Am J Kidney Dis. 2013 Oct;62(4):730-7. Clinical Predictors Associated With Proton Pump Inhibitor-Induced Hypomagnesemia. Am J Ther. 2013 Jul 10. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert Rev Clin Pharmacol. 2013 Jul;6(4):443-51. Effects of proton pump inhibitors and electrolyte disturbances on arrhythmias. Int J Gen Med. 2013 Jun 28;6:515-8 Hypomagnesaemia. Drug Ther Bull. 2013 Mar;51(3):33-6.

Other Acid Blocking Medications: "H2 Blockers These acid-reduction medications block production of stomach acid by about 65-70%. They present less overt risk of impairment of vitamin B12 from natural food sources than acid reduction with PPIs, but supplementation in pill or other supplement form is strongly advised. This is because supplementation is very safe, cheap and easy to do, whereas B12 inadequacy can be very damaging and inadequacy of this critical nutrient is rarely recognized before injury has occurred.

Chronic Antibiotic Use

There are many types of antibiotics and many different reasons for using them. For example, conditions associated with chronic use of antibiotics include: spinal cord injury including spina bifida, and others at risk of kidney/urinary tract infections, tuberculosis, cystic fibrosis, inflammatory bowel disease, chronic ear infection, immune system issues (e.g. HIV/AIDS, hypogammaglobulinemia, etc.) and severe acne.

General Nutrition Issues for All Chronic Antibiotics:

Vitamin K

Antibiotics impair the expected vitamin K production by intestinal bacteria. This is not new. **However, that source is now known to be generally poorly available for everyone.** This is fairly new. [Just since 2006.]

However, people taking chronic antibiotics will be getting absolutely none from that source regardless. Generous vitamin K supplementation is recommended for everyone, and for this population in particular. Vitamin K is very NON-toxic, although people often assume that it is toxic because it is fat soluble. No upper end of safety has ever been established for it because no one has ever taken enough to cause problems. [The only safety issue involving vitamin K is the (often misunderstood) interaction with the drug warfarin (Coumadin) which will be discussed later.]

The current recommended intake of vitamin K for the healthy population appears to significantly underestimate the amount needed to assure optimal blood levels of this vitamin. Vitamin K deficiency contributes to osteoporosis, arterial calcification, kidney calcification, risk of diabetes and certain cancers.

Note that these health risks all are increased long before coagulation time is effected so one's coagulation time is not a good way to monitor a person's vitamin K adequacy. [Please see my see "My Current Top Five Easy Ways to Improve Your Family's Nutrition (subject to change at any moment!" or my "Vitamin K" papers for more detail.

Impairment of Absorption of Folic Acid

The 1998 introduction of fortification of grain products with a well-absorbed form of folic acid in the US improves the odds of preventing some of the folic-acid related problems. However, requirements continue to be higher for people chronically taking antibiotics than for people not using these medications. Generous supplementation is recommended. It is also safe, easy and inexpensive. As described earlier, the results of folic acid inadequacy includes birth defects, poor DNA production, depression, high homocysteine level, increased risk of heart disease andstroke, and serious neurologic damage.

Two Specific Interactions of Interest:

Tetracycline

Tetracycline reduces absorption of folic acid, but B vitamins in general also reduce absorption of tetracycline, so they should not be taken at the same time. As always, this does not mean that a person should be made to be vitamin deficient in order to optimize drug absorption. It just means that attention should be paid to maintaining both general vitamin adequacy and efficacy of the tetracycline dose used.

Isoniazid (Nydrazid, Laniazid)

Vitamin B6 (pyridoxine) levels in the blood are decreased by these TB medications. It used to be a well-known interaction when tuberculosis was very common, but it fell off our radar when TB became quite rare. Only we old guys remember it from that time period. However, TB is now back (for a variety of reasons) and the awareness of vitamin B6 supplementation also needs to come back whenever these medications are used. Some of the neurologic and birth-defect symptoms described as side effects of isoniazid appear to be related to the relative vitamin B6 deficiency associated with its use.

In any case, assuring adequacy of vitamin B6 is very important in this situation, and as is the case for other B vitamins, this can be done easily, cheaply and safely. It does not impair the efficacy of the drug. Pyridoxine is known to be safe at up to 200 mg/day. The usual recommended intake is between 1.5-2 mg/day. It is usually given at 10-50 mg/day to patients on isoniazid.

There are many interactions with nutrition seen with chronic antibiotic use, but this is a quick overview so I have focused on only a few examples. Health care professionals will want to familiarize themselves with the ones they see often in their practice and that will be far more than can be covered here. Luckily, this kind of specific information is now easy to get on reliable sites on the Internet.

Anti-coagulants: Warfarin (Coumadin)

Since 2005, our understanding about the role(s) of vitamin K and the natural means by which we get it have undergone tremendous change. As described earlier (in the section on antibiotics,) it is now known that there are many important functions of vitamin K besides the well-recognized role in blood coagulation, making us aware that inadequacy of the vitamin is very detrimental to health. For example, vitamin K is a cofactor necessary to activate osteocalcin (formerly called calcitonin) to allow calcium to be moved from the bloodstream into the bones. Failure to manage calcium levels in blood and bone contribute to a variety of health problems.]

Additionally, during this same period our assumptions about the availability of vitamin K made by intestinal bacteria have changed markedly. And even the importance of assuring ADEQUACY of vitamin K (and not just consistency of intake) as a key factor in the safety of warfarin use has now been shown. That is, persons with adequate/normal vitamin K status have been shown to be far less vulnerable to extremes of coagulation volatility that is a danger associated with the use of this drug.

Misunderstandings about the interaction of warfarin with vitamin K are extremely common and they result in very serious health consequences. This particular anticoagulant works by interfering with the availability of vitamin K as a cofactor in the cascade of events that produces a blood clot. **The official recommendations from the manufacturers are that people should take a consistent and adequate amount of vitamin K.**

A consistent and adequate vitamin K intake will do much to prevent volatility in blood clotting that can be associated with wide swings in vitamin K intake. That is, maintaining adequacy of vitamin K seems to buffer the degree of variation in coagulation associated with daily differences in vitamin K intake.

However, the official intake recommendation is very often misinterpreted by users of the medication and by health professionals, and the belief continues to be commonly expressed that one should "avoid all sources of vitamin K." Some people are even told that they should avoid taking any vitamins … even if the vitamin product did not contain vitamin K! (Until very recently, MANY common multivitamin brands did NOT contain vitamin K.)

Interestingly, as noted above, consistently providing at least a daily standard amount of vitamin K by supplementation actually makes the drug safer to use, especially in elderly people. Additionally, it works toward preventing the serious (but not uncommon) consequences of accidentally (or intentionally) inducing a **Vitamin K deficiency that results in increased risk of the following health problems:**

Osteoporosis
Calcification of kidneys and kidney stones
Artery damage (Calcification of arteries increased arterial inflammation and risk of plaque build-up, high blood pressure and varicose veins.)
Cancer of the liver and colon
Type II Diabetes
Pre-eclampsia in pregnancy

The Role of Vitamin K in Blood Clotting:

Remember that vitamin K does not MAKE you clot your blood …
It just needs to be available if you WANT to clot your blood.
It is a tool needed by one of the enzymes in the cascade of events leading to clot formation.

[If it MADE people clot their blood, we could expect to have big problems after eating a big spinach salad.
Vitamin K is just a cofactor (a tool) needed to do the job, not the thing that initiates the process.]

Also: The only anticoagulant medication that works by making vitamin K unavailable is warfarin … all the other products work differently so there is absolutely no need to limit vitamin K intake with their use.

Recommendations for people not using warfarin
(that is … almost everyone):

Take a generous amount of vitamin K. A good daily amount would be at least twice the current recommendation for most healthy people (because that level appears to be set too low to assure optimal blood levels.) Dark leafy greens are great foods for many reasons, and they are the richest dietary source. Supplemental vitamin K is an option as well. Remember that vitamin K is NOT toxic and no upper tolerance level has ever been set because no one has ever had problems. **The ONLY vitamin K safety issue is the potential interaction with the drug warfarin.**

Recommendations for people who may be going to start taking warfarin:

Before starting the drug do as described above for people not on the medication to assure an adequate vitamin K level. The doctor will then set the appropriate drug level needed to control coagulation for a person who also now has adequate vitamin K status. [This prevents setting the drug prescription based on a person's unrecognized inadequate vitamin K level.]

Then continue to take in a consistent and adequate amount as a vitamin K supplement while on the drug. **Now, many doctors are regularly prescribing a daily vitamin K supplement when they initiate any warfarin prescription in order to reduce the health risks associated with this medication.**

Recommendations for people currently taking warfarin:

Do not make any changes in your vitamin K intake without the approval of your physician. If your vitamin K level is low, he/she will want to

gradually "walk up" the vitamin K intake until you are in the healthy range. This can be monitored just as it was when one initially starts on the medication. Abrupt changes from low to normal-high vitamin K are not safe when one is on warfarin. There may be other factors to consider in a person's particular situation.

Once the low vitamin K level is corrected by the physician, he/she will want the patient to continue to take in a consistent and adequate amount as a vitamin K while on the drug. As noted, this will often include a prescription for daily vitamin K supplement in order to maintain the decreased health risks. Additionally, there is no reason to discontinue assuring a consistent and adequate amount of vitamin K even if if the warfarin is discontinued at some point.

An additional reason to avoid banning dark leafy greens from the diet:

Inducing a vitamin K deficiency by banning vitamin K-rich foods also **decreases intake of lutein,** the dark green pigment of the foods that provide vitamin K. It is a potent antioxidant with important roles in prevention of oxidative damage to cell membranes, especially in macular degeneration and the development of complications of diabetes.

Vitamin K-rich foods are naturally very low in fat and calories, and they are very "nutrient dense." Removing them unnecessarily from people's diet is not in their best interests. Similarly, telling people to "stop taking a multivitamin to avoid taking in vitamin K" means that one has just removed all the other nutrients they would have received by taking the multivitamin.

This includes 400 iu vitamin D, and although the 400 iu amount in the multivitamin is not even sufficient as a maintenance level in terms of blood vitamin D level, in many people it may be the ONLY vitamin D they do get. It is especially <u>not</u> benign to remove this source of vitamin D and other nutrients such as vitamin B12 in a form that is absorbed best by elderly people or those on PPIs.

Other types of anti-coagulants

Other anticoagulants (e.g. Plavix, Aspirin, Aggrinox) do not work by means of interacting with vitamin K. **They operate entirely differently, in a way that does not involve tinkering with vitamin K availability. That means that there is absolutely no reason at all to restrict vitamin K for these patients.**

Encourage intake of foods rich in vitamin K for many reasons, including the other nutrients and lutein that are well-represented in those foods. A multivitamin with minerals that also includes vitamin K is a very good idea as well, in part because there are a lot of people who don't go anywhere near those dark leafy greens even if we nag at them. Additionally, it appears that the amount of vitamin K needed to assure a healthy blood level is higher than 90-120 mcg, the amount currently recommended for healthy people.

Diuretics: Furosemide (Lasix)

Magnesium is a mineral cofactor in over 300 metabolic pathways, including energy and protein metabolism, bone health and nervous system function. Use of furosemide (Lasix) increases losses of potassium and also magnesium. The potassium part is well known to health professionals so I won't address it here, but **the magnesium losses are much less well known.** At a cellular level, potassium metabolism cannot operate normally in the absence of adequate magnesium.

The foods that are well-known to be rich in potassium (e.g. potatoes, milk, bananas, orange juice, etc.) do not happen to be rich in magnesium. The best foods sources of magnesium are the part of the plant that will be "the baby plant" … that is, the part that is a seed, bean, germ, or nut designed to grow if planted. Increasing intake of these foods can be very helpful for many health reasons. These include decreasing risk of developing Type II diabetes, improving management of diabetes, and minimizing leg cramps.

The fairly recent recognition of these foods as the best natural magnesium sources and the importance of magnesium adequacy is a main reason why "whole grains" … the kind that still have the **germ** included … and eating nuts are being encouraged.

Most multivitamins contain 0- 25% of the recommended magnesium intake. (Most contain zero potassium, by the way.) For people not on furosemide, the amount of magnesium provided in a multivitamin may be sufficient **if** food magnesium sources are generally good. However, **it is unlikely to be sufficient if furosemide is in the picture as well.**

In this context, supplementation of a separate magnesium oxide or magnesium chloride to provide about 400 mg/day more is a good idea for people on this medication, unless the person has poorly functioning kidneys. Four hundred is just the usual recommended amount for healthy people and readily available over the counter … it is not a high "therapeutic" level.

[Note that magnesium sulfate and magnesium citrate are poorly absorbed sources of magnesium, and they contribute to loose stools. That is why they are used for constipation problems and for cleansing the bowel prior to having a colonoscopy. The unabsorbed particles attract water to the intestine. They are not as effective as dietary supplements.]

The addition of a medication that increases urinary losses of magnesium can result in very low levels. Consider that **magnesium intake is generally low in many Americans.** In NHANES research (the National Health and Nutrition Examination Survey) done at the CDC every ten years, it has been found that most Americans obtain less than 2/3 of the recommended amount of magnesium. This is not good because, as noted, **magnesium inadequacy contributes to diabetes** (because insulin receptors are magnesium dependent) and also to energy metabolism in general, all protein metabolism, and nerve function. It is hugely important in pregnancy.

At the same time, we rarely look closely at a nutrient that is not easy to evaluate meaningfully. For example, **blood magnesium levels in general do not reflect cellular magnesium levels**, so an "OK" blood magnesium level does not tell us about magnesium intake adequacy. The blood Mg level is controlled by the kidney, and it may stay in the normal range even if cells are not getting enough for optimal functioning.

My experience has been that most people on diuretics are given advice from health professionals about potassium and about eating bananas specifically (courtesy of a successful advertising campaign of the Chiquita people some years back.) But the magnesium loss is often left out of the conversation in part because it is hard to measure with a lab that identifies cellular adequacy. The other reason is that people have not been told what foods are rich sources of magnesium and how to assess magnesium intake meaningfully.

The practical answer to determining a person's magnesium intake is to ask about the amount of those "baby plant" foods that a person eats. Regularly eating a good amount of nuts, seeds, legumes (like beans, peanuts, peas and lentils) and whole grains is the best indication that one has a healthy dietary magnesium intake.

[The Harvard Women's Health Study found that eating an ounce of nuts or peanuts four times a week or more was associated with 25% less risk of developing type II diabetes in a 16 year period.] These foods are also rich sources of other nutrients in addition to magnesium.]

Asking about these "baby plant" foods is key because details of a person's actual diet are rarely evaluated in the brief amount of time allotted to a clinic visit. Just saying "eat a balanced diet and exercise!" does not provide enough specific information to protect people from the increased risk of magnesium inadequacy associated with this medication.

[By the way … contrary to what many of us learned, bananas are NOT the top source of dietary potassium. Potatoes are actually the highest (Mnemonic device: potato = potassium) and milk, orange juice and other foods are excellent sources as well. Maybe there should be more marketing of potatoes from a Chiquita Banana-like spokesperson … maybe Mr. PotatoHead. ☺]

Encouraging a generous intake of these same foods (along with a multivitamin with minerals) is especially important for your patients on furosemide or any other diuretic that is described officially as causing potassium loss in the urine. If the patient is unable or unwilling to eat a generous amount of these foods, consider adding a 400-500 mg magnesium supplement as described (unless there is a question of kidney problems.)

Miscellaneous

Methotrexate

Methotrexate and Folic Acid:

Some medications are used in the treatment of many different conditions. One of these is methotrexate, which is used in treating **cancer** and also for **inflammatory diseases** like rheumatoid arthritis and psoriasis.

One problem with methotrexate use is that in spite of its effectiveness in treating certain health conditions, people often have to stop taking it because of severe side effects. Happily, a generous intake of **folic acid** has been shown to minimize some of the side effects to the degree that people do not have to discontinue using an effective medication.

The amount needed for this positive methotrexate-tolerance effect is more than what one could eat from food or obtain from a multivitamin, so usually one would get a prescription for the higher dose needed. The much more generous folic acid amount in the prescription pill is still very small and easy to take. The folic acid needs to be provided in supplement form: pills, drops, gel caps, etc. There is just not enough in food ... even if you are the King or Queen of Kale. (Kale is the richest food source.)

Also, some individuals have a genetic pattern (like one called the MTHFR gene) that makes them have **difficulty getting it absorbed in the food form.** The recognition of this genetic folate problem was the reason they added some in a more digestible/ absorbable form to all grain products in America in 1988. Since then we have had a country-wide reduction in folic acid inadequacy problems like stroke (15% reduction) and a 50-70% reduction in the incidence of spina bifida (a serious birth defect.) There was a 50% over-all decrease, but some at-risk populations had an even more protective response! Wow!

However, even though they added a more digestible/absorbable FORM, the AMOUNT is still aimed at achieving a total intake of about the RDA for healthy people. That is, 400 micrograms ... and not even close to the 7,000 micrograms/week that was found to be protective against intolerance of methotrexate in the study described below.

That TREATMENT amount obtained by prescription is still just a teeny little pill and it is not expensive. As an example, here is the conclusion of one recent study showing that methotrexate side effects were better tolerated when generous folic acid was also provided:

Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis.

J Rheumatol. **2014** Jun;41(6):1049-60.

"Conclusion: The results support a protective effect of supplementation (a starting dose of ≤ 7 mg weekly) with either folic or folinic acid for patients with RA during treatment with MTX

There was a clinically important significant reduction shown in the incidence of GI side effects and hepatic dysfunction (as measured by elevated serum transaminase levels), as well as a clinically important significant reduction in discontinuation of MTX treatment for any reason."

Methotrexate and Omega-3 Oils:

Another approach to prevent some of the side-effects of using methotrexate is to **replace some omega-6 fats with omega-3 fats** to decrease the inflammatory strength of prostaglandins in order to **decrease inflammation associated with intolerance of the medication.** For example, oral omega-3 fats (precursors of less inflammatory prostaglandins) prevented mucosal injury and improved intestinal recovery after methotrexate-induced injury in rats. Here's a recent study:

Reversal of severe methotrexate-induced intestinal damage using enteral n-3fatty acids.

Br J Nutr. **2013** Jan 14;109(1):89-98

"Growing evidence suggests that n-3 PUFA and their specific lipid mediators can reduce the activity of inflammatory processes. In the present study, we evaluated the effects of oral n-3 PUFA supplementation on intestinal structural changes, enterocyte proliferation and apoptosis during methotrexate (MTX)-induced intestinal damage in the rat. … **Thus, the treatment with oral n-3 PUFA prevented mucosal injury and improved intestinal recovery following MTX-injury in rats."**

However, it is now recognized there is a significant number of people who are unable to convert vegetable-oil omega-3 fats (like in flax oil and canola oil) into the important active substances that more directly help with inflammation (EPA and DHA.)

For that reason, it is reasonable to take the omega-3 oil in the "ready-to-operate" EPA and DHA form. (As a memory jogger, I always think of EPA as standing for "Environmental Protection Agency … it protect one's internal environment.) This is the form in **fish oil and krill oil**.

The key content in fish or krill oil is ready-made EPA and DHA, oils NOT found in any plant omega-3 oils. Also, note that a fish oil capsule is just a FOOD wrapped up in a capsule because it tastes bad. (You could certainly take tablespoons full of cod liver oil if you prefer!) It is just an edible oil, like the oil found in salmon or other fatty fish like herring or sardines.

Ounce for ounce, most other fish provide significantly less oil so they are not as useful in terms of obtaining EPA and DHA. For that reason, to obtain a very generous intake of these special oils, one must eat A LOT of salmon, herring and sardines if fish/ krill oil supplementation is not in the picture.

What if the person getting the fish oil supplement did not need the special forms of oil just at that moment? Would that person experience an overdose? Answer: No. One would just store the oil as fat, use it to make cell membranes, or burn it for fuel like any other fat. It is not a drug. It is available over-the-counter. Additionally, it will not require a way-bigger-than-usual dose the way folic acid did as described above. But a regular intake is reasonable ... like taking one or two several times a day during treatment (with a doctor's permission, of course.).

How much is likely helpful? The amount of fish oil for people with a variety of common health problems (heart disease, diabetes, arthritis, and others) is more than the amount for healthy adults in general. The dosage for those medical conditions is often suggested at 2-to-4 1-gram capsules per day. However, **for a person about to start taking methotrexate**, one's doctor might want a more generous "up-front" dosage for a person who rarely eats fish and who has not been regularly taking fish or krill oil. (Won't hurt … might really help!)

One can also use krill oil instead of fish oil to get EPA and DHA. Krill capsules are tinier and a bit more expensive, but for some folks the krill form is less likely to make them burp fish fumes. (I use regular ones because they don't bother me, but my husband uses krill oil because fish oil does come back to haunt him. People are different.) There also may be a bit more availability of the DHA component provided by krill oil compared with fish oil, and DHA has important roles to play in brain health as well as its role in the inflammation picture. [I remember the DHA/Brain link by thinking of DHA as DUH or Homer Simpson's "D'oh!" … not too clever but it works for me. ☺]

HMG-CoA-Reductase-Inhibitors (Statin Drugs)

These medications are designed to lower "high cholesterol" in an effort to decrease risk of cardiovascular disease. They essentially work by putting a thumb on the first enzyme (HMG-CoA-Reductase) that starts up the chain of events by which people make cholesterol.

Our "home-made" cholesterol accounts for much more of one's blood cholesterol than the cholesterol eaten in foods, so the thinking has been that significantly decreasing cholesterol production could be very helpful to folks with high cholesterol levels.

However, it is now becoming apparent that the pathway we inhibit with statin drugs is involved in making many things besides just blood cholesterol. Additionally important is the fact that cholesterol itself does many things that are not related to trying to kill you. For example, there are many very important things that one makes out of cholesterol, including all cell membranes, myelin for efficient nerve messaging, and bile for digestion/absorption of fats.

Also, some hormones are made out of cholesterol, including aldosterone and vitamin D, and male and female hormones like testosterone, estrogen and progesterone. Failure to make any of these important substances could certainly have significant negative health consequences.

The **drug/nutrient interaction** highlighted here, though, is the more recent discovery that **statins may interfere with production of a substance called CoQ10.** [Another name for CoQ10 is "ubiquinone" or "ubiquinol." The name comes from the word "ubiquitous," meaning "all over the place"… because this substance is literally **needed all over the body**.]

CoQ10 is involved in energy metabolism pathways in the mitochondria, and it is also a very potent protective antioxidant. It does not meet the official definition of being an actual "vitamin" because the healthy human body can (normally) make enough on its own. Like carnitine, it is considered to be a "conditionally essential" substance … and one of the "conditions" that makes it become essential appears to be statin drug use.

However, it is becoming apparent that **some individuals DO have higher than usual requirements and the amount they can make simply does not meet their needs**. In that situation, those folks would benefit from supplementation of CoQ10. This includes people with inflammatory diseases like diabetes, MS, arthritis, macular degeneration, and conditions involving impaired mitochondrial energy production.

The new issue of interest here is that it appears that while statin use decreases production of cholesterol, it also decreases production of CoQ10. That can interfere with protection from free radical damage, and it can also affect energy metabolism. Some of the side effects like muscle soreness, injury and weakness associated with statin drugs may be related to the relative loss of CoQ10 production. Supplementation is a good idea for several reasons if statins are given. Supplementing CoQ10 is very benign, but CoQ10 inadequacy is not. [On a related note about statin-related myalgia: It is also now known to be associated with other nutrition factors such as low vitamin D status.] (Vitamin D and Statin-Related Myalgia .http://www.medscape.com/viewarticle/876941_prin)

Since CoQ10 is not classified as "a vitamin," there is no RDA established that would give a guideline of how much might be "needed by healthy people." Recommendations regarding dosage are subject to change as more research becomes available, but just to give an idea, **here are some of the guidelines <u>we</u> use when CoQ10 is needed for our patients who have mitochondrial diseases and also those with Prader-Willi Syndrome.**

(One could also check out any of the reports shown on the next page to see what is now being used as a therapeutic dose in the wide variety of health applications.)

Amount: 60 mg/day minimum (for children I usually use 100 mg, but research with adults in many areas has seen more benefit with higher doses (e.g. 200-600 mg) without any problems. CoQ10 is an important cofactor and potent antioxidant, and it is not dangerous.

Absorption: Best absorbed if administered with a meal that normally **contains some fat**.

Timing of administration: Divided dosage is ideal, but it is hard to prevent loss of product activity if the capsule is exposed to oxygen after a partial use. One approach would be a 30mg capsule twice daily if available in that form. Otherwise giving the 60 mg capsule all at once is likely the next best option. More forms will be certainly be developed in the near future.

Time to observe effects: Some people take up to eight weeks to demonstrate significant effects … others are much faster. Ideally, a trial should go for 4-6 months before deciding that the CoQ10 was not helping a symptomatic patient in some way, including helping with energy, muscle pain and/or muscle function in patients using statins.

It is not dangerous to take CoQ10 as described above … or even in larger amounts NOT described above. What is NOT safe is to fail to consider adding it for a person who is having tolerance problems with statins.

As always, the scientific reports are conflicting, often because of study design limitations. Additionally, there appear to be genetic variables that effect how useful CoQ10 is in patients with statin-induced myopathy. So, (of course) lots more research (and better-designed research) is needed to figure this out.

The key point at this time is to be aware that impaired CoQ10 production (or increased intake requirements such as might result from the use of statin drugs) is an emerging issue likely to be very important in many health conditions with effects on many systems besides just the myopathy questions currently on our radar.

Below are just the recent articles (mostly2016) quickly gathered from PubMed that illustrate the scientific interest in **supplemental CoQ10 for wide range of medical conditions**. (In other words … I am NOT making this up!)

Recent research on supplemental CoQ10 for wide range of health conditions (2014— 4/2016)

2016

Protective effect of Co-enzyme Q10 On doxorubicin-induced **cardiomyopathy** of rat hearts. Environ Toxicol. **2016** Apr 18.

An Improvement of Oxidative Stress in **Diabetic** Rats by Ubiquinone-10 and Ubiquinol-10 and Bioavailability after Short- and Long-Term Coenzyme Q10 Supplementation. J Diet Suppl. **2016** Apr 11:1-13.

Coenzyme Q biosynthesis in **health and disease**. Biochim Biophys Acta. **2016** Apr 7

Effects of coenzyme Q10 supplementation on C-reactive protein and homocysteine as the inflammatory markers in hemodialysis patients; a randomized clinical trial. J Nephropathol. **2016** Jan;5(1):38-43.

Middle-Term Dietary Supplementation with Red Yeast Rice Plus Coenzyme Q10 Improves Lipid Pattern, Endothelial Reactivity and Arterial Stiffness in Moderately Hypercholesterolemic Subjects. Ann Nutr Metab. **2016**;68(3):213-9.

Combination therapy with coenzyme Q10 and trimetazidine in acute **viral myocarditis** patients. J Cardiovasc Pharmacol. **2016** Apr 2.

Superoxide- and NO-dependent mechanisms of **antitumor and antimetastatic** effect of L-arginine hydrochloride and coenzyme Q10. Exp Oncol. **2016** Mar;38(1):31-5.

Coenzyme Q10 and **Heart Failure**: A State-of-the-Art Review. Circ Heart Fail. **2016** Apr;9(4):e002639

Relationships between **Cognitive Function and Cerebral Blood Flow**, Oxidative Stress and Inflammation, in Older Heart Failure Patients. J Card Fail. **2016** Mar 18.

Mitochondrial respiration in the platelets of patients with **Alzheimer's disease**. Curr Alzheimer Res. **2016** Mar 14.

Coenzyme Q10 Supplementation Modulates NFκB and Nrf2 Pathways in **Exercise Training**. J Sports Sci Med. **2016** Feb 23;15(1):196-203.

Coenzyme Q10 Exerts Anti-Inflammatory Activity and Induces Treg in **Graft Versus Host Disease**. J Med Food. **2016** Mar;19(3):238-44..

Multivitamins and minerals modulate whole-body energy metabolism and cerebral blood-flow during **cognitive task performance**: a double-blind, randomised, placebo-controlled trial. Nutr Metab (Lond). **2016** Feb 11;13:11.

A Therapeutic Insight of Niacin and Coenzyme Q10 Against **Diabetic Encephalopathy** in Rats Mol Neurobiol. **2016** Feb 11.

Do Medications Commonly Prescribed to Patients with **Peripheral Arterial Disease** Have an Effect on Nutritional Status? A Review of the Literature. Ann Vasc Surg. **2016** Apr;32:145-75.

Mitochondrial dysfunction in inherited **renal disease** and acute **kidney injury**. Nat Rev Nephrol. **2016** May;12(5):267-80.

Drugs indicated for mitochondrial dysfunction as treatments for **acute encephalopathy** with onset of febrile **convulsive status epileptics**. J Neurol Sci. **2016** Jan 15;360:57-60.

Coenzyme Q10 prevents **hepatic fibrosis**, inflammation, and oxidative stress in a male rat model **of poor maternal nutrition and accelerated postnatal growth**. Am J Clin Nutr. **2016** Feb;103(2):579-88.

Combination therapy with metformin and coenzyme Q10 in murine experimental **autoimmune arthritis**. Immunopharmacol Immunotoxicol. **2016** Apr;38(2):103-12.

Coenzyme Q10 Attenuates High Glucose-Induced Endothelial Progenitor Cell Dysfunction through AMP-Activated Protein Kinase Pathways. J **Diabetes** Res. **2016**;**2016**:6384759.

Coenzyme Q10 Supplementation Prevents **Iron Overload** While Improving **Glycaemic Control** and **Antioxidant Protection** in Insulin-Resistant Psammomys obesus. Biol Trace Elem Res. **2016** Jan 18.

Coenzyme Q10 defects may be associated with a deficiency of Q10-independent **mitochondrial respiratory chain** complexes. Biol Res. **2016** Jan 8;49(1):4.

Topical Coenzyme Q10 Eye Drops as an Adjuvant Treatment in Challenging Refractory **Corneal Ulcers**: A Case Series and Literature Review. Eye Contact Lens. **2016 Jan 16.**

Effect of Coenzyme Q10 Supplementation in **Statin-Treated Obese** Rats. Biomol Ther (Seoul). **2016** Mar 1;24(2):171-7

Statins accelerate disease progression and shorten survival in SOD1G93A mice [**ALS**]. Muscle Nerve. **2016** Jan 21.

Cognitive remission: a novel objective for the treatment of major **depression**? BMC Med. **2016** Jan 22;14(1):9.

Cerebellar ataxia and severe muscle CoQ10 deficiency in a patient with a novel mutation in ADCK3. Clin Genet. **2016** Jan 27.

Serum Levels of Coenzyme Q10 in Patients with **Multiple System Atrophy**. PLoS One. **2016** Jan 26;11(1):e0147574.

Additive enhancement of **wound healing in diabetic** mice by low level light and topical CoQ10. Sci Rep. **2016** Feb 2;6:20084.

Acute Hypoglycemia Induces **Painful Neuropathy** and the Treatment of Coenzyme Q10. J Diabetes Res. **2016**;**2016**:4593052.

Accelerated Regeneration of ATP-level After **Irradiation** in Human skin Fibroblasts by Coenzyme Q10. Photochem Photobiol. **2016** Mar 6.

Potency of pre-post treatment of coenzyme Q10 and melatonin supplement in ameliorating the impaired fatty acid profile in rodent model of **autism**. Food Nutr Res. 2016 Mar 3;60:28127

Statin-associated cerebellar ataxia. A Brazilian case series. Parkinsonism Relat Disord.**2016** Apr;25:97-9

Coenzyme Q10 Levels Are Decreased in the Cerebellum of **Multiple-System Atrophy Patients**. PLoS One. **2016** Feb 19;11(2):e0149557

Coenzyme Q10 redox state predicts the concentration of **c-reactive protein** in a large caucasian cohort. Biofactors. **2016** Feb 23.

2014- 2015

The Effect of Coenzyme Q10 Supplementation on Pro-Inflammatory Factors and Adiponectin in Mildly **Hypertensive** Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. Int J Vitam Nutr Res. **2015**;85(3-4):156-64.

Glutaredoxin mediated redox effects of coenzyme Q10 treatment in **type 1 and type 2 diabetes patients**. BBA Clin. **2015** Jun 10;4:14-20..

The Interaction Between Statins and **Exercise**: Mechanisms and Strategies to Counter the Musculoskeletal Side Effects of This Combination Therapy. Ochsner J. **2015** Winter;15(4):429-37.

The suppressive effect of dietary coenzyme Q10 on mitochondrial reactive oxygen species production **and oxidative stress** in chickens exposed to **heat stress**. Anim Sci J. **2015** Dec 28.

Prophylactic role of coenzyme Q10 and Cynara scolymus L on **doxorubicin-induced toxicity** in rats: Biochemical and immunohistochemical study. Indian J Pharmacol. **2015** Nov-Dec;47(6):649-56.

Integrative Therapies and **Cardiovascular Disease in the Breast Cancer** Population: A Review, Part 1. Integr Med (Encinitas). **2015 Aug;14(4):22-9.**

Delayed Posthypoxic Leukoencephalopathy: Improvement with Antioxidant Therapy. Case Rep Neurol. **2015** Dec 24;7(3):242-6.

Coenzyme Q10 as a treatment for fatigue and depression in **multiple sclerosis** patients: A double blind randomized clinical trial. Nutr Neurosci. **2015** Jan 20.

Effects of coenzyme Q10 on **statin-induced myopathy**: a meta-analysis of randomized controlled trials. Mayo Clin Proc. **2015** Jan;90(1):24-34.

Association between serum level of ubiquinol and NT-proBNP, a marker for **chronic heart failure**, in healthy elderly subjects. Biofactors. **2015** Jan 2;41(1):35-43.

Circulating levels of reactive oxygen species in patients with nonproliferative **diabetic retinopathy** and the influence of antioxidant supplementation: 6-month follow-up Indian J Ophthalmol. **2015** Jan;63(1):9-14.

Administration of CoQ10 analogue ameliorates dysfunction of the mitochondrial respiratory chain in a mouse model of **Angelman syndrome**. Neurobiol Dis. **2015** Feb 12;76C:77-8

Gastroprotective effects of CoQ10 on **ethanol-induced acute gastric lesions**. Bratisl Lek Listy. **2015**;116(1):51-6.

Statins stimulate atherosclerosis and heart failure: **pharmacological mechanisms.** Expert Rev Clin Pharmacol. **2015** Mar;8(2):189-99.

Coenzyme Q10 and **spinocerebellar ataxias**. Mov Disord. **2015** Feb;30(2):214-20.

Coenzyme Q10 supplementation decreases **statin-related mild-to-moderate muscle symptoms**: a randomized clinical study. Med Sci Monit. **2014** Nov 6;20:2183-**8.**

Coenzyme Q10 as a therapy for **mitochondrial disease**. Int J Biochem Cell Biol. **2014** Apr;49:105-11.

CoQ10-containing eye drops prevent UVB-induced **cornea** cell damage and increase cornea wound healing by preserving **mitochondrial** function.. Invest Ophthalmol Vis Sci. **2014** Oct 9;55(11):7266-71.

Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with **multiple sclerosis**: a double blind, placebo, controlled randomized clinical trial. Nutr Neurosci. **2014** Jan 10.

Interestingly**, <u>combinations</u> of CoQ10, carnitine and alpha-lipoic acid** (and other combinations) are being used together in researching a variety of health conditions with some evidence of improved effectiveness of combined supplementation above that seen from supplementing any one of them alone.

Combinations of this kind are sometimes called **"mitochondrial cocktails"** which can sometimes help with energy metabolism problems even when the specific mitochondrial problem or defect is unclear. This is an active … and promising … area of scientific research.

CoQ10, carnitine and alpha-lipoic acid have several features in common:

1. All are known to be critical substances **required for different aspects of energy metabolism** in the mitochondria. For example, operation of the electron transport chain, the TCA cycle, glycolysis and long-chain fatty acid transport into the mitochondria for beta-oxidation all require at least one of these three substances.

2. All are **potent antioxidants** that protect against oxidative damage to cell membranes all over the body. They are all much more potent as antioxidant protectors than vitamins or minerals with known antioxidant properties.

3. (**Until recently**) all were **presumed to be made by everyone in adequate amounts** to meet their needs and therefore they have been labeled "non-essential" substances. Now it is clear that in certain circumstances they are in fact actually "essential" and need to be taken in ready-made. That is why they are called "conditionally essential" substances. There are apparently many such "conditions," including diabetes, Down Syndrome, and autoimmune problems.

4. All three are **generally benign substances to supplement in healthy people***.

***As with all supplements, please check with your physician to be sure there is no reason to avoid any of them if you have a particular health problem or take medications.**

After all, as this paper illustrates, nutrients and other cofactors can and do have the potential to interact with medications and health conditions, in both positive and negative directions.

Stay tuned!