May 2003 Issue | David J. Musnick, MD, MPH

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Welcome to *Functional Medicine Update* for May 2003. I begin with an interesting clinical anecdote. You may wonder why anyone would want to read all the research papers we have cited over the years of *FMU*. Sometimes it is hard to know exactly how to answer that question, but there are a few times when it is good to have access to that information when you need it. The following case history is an example.

Recently, a patient who was considering elective surgery consulted us. This gentleman was over 70 years old. He had been rejected for surgery until he could bring his potassium levels up. He was not on any anti-hypertensive medication and his diet appeared to be adequate in potassium. His low serum potassium level caused him to be considered a surgical risk, and the surgery would not be allowed until he got his potassium up into a normal range. The question was raised as to how one raises potassium levels.

The simple assumption would be that, if you have low blood levels of a nutrient, you must not be getting enough of that nutrient in your diet. The treatment of choice for low potassium would be to give more potassium-rich foods, and the food that always tops the list is bananas. The patient was advised to eat a lot of bananas, and he did so because he wanted to have the elective surgery. In spite of all the bananas he ate, however, his potassium levels did not increase.

Serum Potassium Levels

Potassium levels in the blood depend on much more than simply the amount of potassium consumed in the diet. They have to do with a complex endocrine control mechanism—the renin angiotensin control mechanism—and its interrelationship with sodium, renal transport, aldosterone, and cortisol, and cortisone. There is a fairly complex network of functional endocrinology that goes into controlling the potassium levels in the blood beyond potassium in the diet.

A group of us discussed how we might assist this gentleman. I remembered an article that appeared in the *New England Journal of Medicine* in October of 1991. I remembered the article as an interesting case report, titled “Licorice-Induced Hypermineralocorticoidism.” I asked if the patient was consuming licorice, because licorice and its phytochemicals can affect 11 β-hydroxysteroid dehydrogenase as an inhibitor.

Effects of Licorice

We sent a report to the man’s attending physician with a question about the patient’s possible licorice consumption. The doctor told the man of our suggestion that licorice consumption could result in low potassium levels. He explained that other phytochemicals in licorice could interfere or affect the way he

retained and metabolized potassium in his body. The patient admitted he liked licorice and ate a few pieces every day.

There is a specific takeaway here in relation to licorice. Then there is a more general question about how we assess nutrients and other substances in the blood and how we reach conclusions about where the problem lies. Let us first deal with the specific of licorice. An article in the *New England Journal of Medicine* describes a case report in which ingestion of excessive licorice can result in sodium and water retention, hypertension, hypokalemia, and suppression of the renin-aldosterone system.[1]

A number of investigators have proposed that licorice inhibits cortisol oxidase. This component of the widely distributed 11 β-hydroxysteroid dehydrogenase system is known to convert cortisol to cortisone. Blocking the conversion of cortisol to cortisone produces a state of apparent mineralocorticoid excess similar to that found in children with congenital 11 β-hydroxysteroid dehydrogenase deficiency.

Genetic Polymorphisms Related to Licorice Sensitivity

Since the 1991 paper was published, we have learned of many polymorphisms and, therefore, although none have yet been identified, it is possible that polymorphisms may occur in the 11 β-hydroxysteroid dehydrogenase. This would mean some people may have much greater sensitivity to the active components in licorice that could have an influence on this enzyme, including glycyrrhetinic acid and its breakdown component glycyrrhizic acid, which is associated with inhibition of 11 β-hydroxysteroid dehydrogenase. Licorice, by inhibiting 11 β-hydroxysteroid dehydrogenase in aldosterone-responsive tissues like the kidney, where it is found in high concentrations, produces high renal levels of cortisol (because it is not converted to cortisone). This cortisol then binds to and activates mineralocorticoid receptors. It has a sort of mimic effect on activation of the mineralocorticoid receptors, producing the state of what appears to be hyperaldosteronism.

When licorice was removed from the gentleman’s diet, his potassium levels went up on his normal diet, without excessive consumption of bananas. He quickly qualified for his surgery, which he underwent successfully.

When you take a person off licorice, the activity of 11 β-hydroxysteroid dehydrogenase is suppressed for about two weeks. The renin-aldosterone system remains low for about two to three months after licorice withdrawal. This can be a powerful effect in certain individuals regarding control of their potassium levels.

Problems with Measuring Serum Levels of Substances

The other more general construct I would like you to consider is that it can be very misleading to assume that blood levels of a substance relate directly to a nutrient in the diet. It does not matter if you are looking at thiamin pyrophosphate as vitamin B1 in the blood, riboflavin as flavin adenine dinucleotide, selenium, iron, or something pertaining to essential amino acids in the blood. The control of those substances in the body depends on much more than the level of intake from the diet. It involves digestion, assimilation, absorption, distribution, transport, uptake, metabolic activation, and excretion. Many steps are involved.

I urge you to be cautious when you observe blood levels of a nutrient. For example, it is possible to have blood levels of vitamin B12 within the normal reference range, but to have inactive or insufficient activity

of a specific enzyme that may require cobalamin for its activity at that level.

Pathological versus Functional Assessment
This is an important distinction between pathological diagnosis, which depends on assessment of blood chemistry, and functional assessment, in which we examine the level of a substance involved with the physiological process that may have various degrees of function or dysfunction. Functional status depends on whether the enzyme is near saturation or far away from saturation with regard to that specific cofactor or coenzyme.

Be sure, when you measure something in the blood, that you know what you are trying to measure. Are you trying to measure for pathology, as you would with the SCOT/SGPT enzymes in liver pathology that when elevated show liver injury? Or are you trying to look at the relative function of a specific enzyme? In that case, an SGOT level that is too low may be as important as an SGOT level that is too high, because low SGOT might indicate low B6 status. Low enzyme activity might be indicative of a different state of physiological function

Extending that argument from the liver and nutrients to the way we expose the liver to all sorts of interesting new substances, I would like to discuss a recent paper that appeared in the *Annals of Internal Medicine.* We have seen in the United States a rapid increase in the number of cases of fulminating liver failure necessitating liver transplants.

Technology and medicine breed their own use. As technology for liver transplant procedures has improved, so have the number of liver transplants. The relative frequency of liver failure and acute liver injury per 100,000 population has increased over the last 15 or 20 years. A number of people have wondered about the cause for this increase. The assumption has been that it is a consequence of cirrhosis related to alcoholism and hepatitis, particularly A and B, which have been thought to be the major cause of acute liver failure requiring a liver transplant.

Increased Acetaminophen Use
The title of the paper I mentioned is “Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States.”[2] The authors of this paper conclude, “Acetaminophen overdose and idiosyncratic drug reactions have replaced viral hepatitis as the most frequent apparent causes of acute liver failure.”

One of the most common over-the-counter drugs in America is acetaminophen. Thinking it is very safe, many people take it as if it were an elixir to palliate certain discomfort without worry about its adverse effects. New studies are learning that reactions to acetaminophen are highly individualized. Liver injury can occur in some people even at the dose suggested on the bottle.

Factors Affecting Acetaminophen Detoxification
How would that occur? From studies we have described in *FMU* over the past few years, you may recall that if a person consumes quite a bit of alcohol, is fasting, or is on a poor-quality diet, those variables can cause depletion of glutathione in the liver. Glutathione is a critical nutrient necessary for the appropriate detoxification of acetaminophen. Individuals with different polymorphisms of detoxification enzymes may require different levels of glutathione in their livers for proper metabolism. If glutathione is not present in adequate amounts in the liver, it cannot properly be conjugated with the intermediate of

acetaminophen, a naphtha quinone intermediate abbreviated NAPQI.

NAPQI
NAPQI is a biotransformed intermediate from the partial metabolism of acetaminophen. It is highly hepatotoxic if it is not properly conjugated with glutathione. If a person is on a poor-quality diet, has been drinking alcohol, or has polymorphisms related to altered sensitivity to glutathione conjugation, that person could, at a normal dose level of acetaminophen, have what is considered an atypical "adverse reaction."

I emphasize that atypical is in the eye of the beholder. If we were to give acetaminophen to that patient on successive days under the same conditions, his or her reaction would not be atypical; it would be reproducible. We could reproduce that same problem. It may be atypical compared to the norm, but it is not atypical relative to the person's own metabolism.

Environmental and Genetic Factors in Detoxification
The apparent cause of toxicity at admission associated with acetaminophen overdose and idiosyncratic drug reactions is related to differences in environment and genes. Toxicity could be the result of a poor-quality diet, alcohol, or other drugs or medications the person is taking concomitantly. Any of these factors, or a combination, increases the need for glutathione for conjugation, and individuals who have altered detoxification have a unique genetic predisposition.

To protect against liver injury, one needs to have adequate levels of the conjugating nutrients and also be able to prevent what is called hepatic oxidative stress, or liver oxidative stress. A paper a few years ago in *International Hepatology Communications* talked about glutathione depletion in chronic hepatitis.[3] It showed that individuals who have hepatitis have increased turnover of glutathione and loss of glutathione reserves that may put them at higher risk to conditions requiring glutathione in the liver for proper detoxification.

Glutathione Need in Hepatitis C
In the abstract of this paper, the authors state, "Thus, in chronic hepatitis C there is a systemic depletion of glutathione that appears to be related to the activity of the disease." This puts a person at higher risk to glutathione-requiring conditions.

This is an important part of the story. Not all individuals have the same hepatic functional status when they take acetaminophen. If you had a low-grade hepatitis virus A, B, or C infection, the quality of your diet was marginal, you occasionally drank wine or beer, and you took acetaminophen, you might set the stage for a much higher risk of liver injury. Protection depends not just on glutathione, but on the array of liver-protective redox substances.

Liver-Protective Substances
This concept is becoming better understood in helping to protect the liver against injury. An editorial in the journal, *Antioxidants & Redox Signaling* discusses redox considerations to prevent hepatic injury and inflammation. Those considerations include the substances we have often heard about that are liver-specific or liver-protective.[4] They include silybin from silymarin (milk thistle), N-acetylcysteine (NAC), which has been found to be liver-protective, and lipoic acid, another liver-protective nutrient.

A number of redox-active nutrients can help support the liver redox protection system. These nutrients can benefit individuals who may have conditions of compromised liver detoxification ability or specific unique genetic risk factors involving low glutathione S-transferase activity. They can also help those who have not been able to produce much glutathione for conjugation. All these are variables that might influence relative risk.

Modifying Liver Risk with Redox-Active Nutrients

Can we modify the potential risk of chronic viral liver infections and liver injury from alcohol, drugs, or even genetic predisposition by consuming diets higher in redox-active nutrients? The answer appears to be yes. Substances on the short list of those protective nutrients include NAC as a precursor to glutathione. It may take 1000 mg or more a day. In a person who has been medicated for alcoholic delirium tremens, you often have to give thousands of milligrams in order to activate their detoxification mechanisms, so the dose may be much higher.

We talked about silymarin and with standardized concentrates high in silybin. The dose here would be in the range of a few hundred milligrams per day. Then we talked about lipoic acid in the range of 1000 or more milligrams per day (or the reduced forms of lipoic acid, dihydrolipoic acid, as another potential liver-protective agent). A high-quality diet, avoiding alcohol, and looking at other drugs that may deplete glutathione stores are also beneficial.

Genetics and Drug Response

The wild card in the story is the genetics of the individual. A recent issue of the *New England Journal of Medicine* contained an extraordinary series of papers, one of which is titled “Genomic Medicine—Inheritance and Drug Response.”[5] The authors of this paper discuss the emerging promise of pharmacogenetics, the study of the role of inheritance of individual variations in drug response, in identifying the right drug and dose for each patient based on each unique detoxification system. This includes age, sex, disease history, drug interactions, and genetic factors.

The concept of inheritance and drug response, or pharmacogenomics and pharmacogenetics, is an expanding field in medicine. I predicted 10 years ago in *FMU* that the concept of detoxification would become a prominent theme in traditional medicine and medical training. I did not, however, recognize how quickly it would occur, with the advent of genomic testing and the discovery and unfolding of the human genome.

Detoxification Polymorphisms

We are starting to see a number of polymorphisms in the detoxification enzyme system. In fact, cytochrome P450 seems to have the greatest degree of genetic polymorphism of any class of enzymes we have found to date, suggesting there might be some cultural, anthropological, and evolutionary reasons why we see such a wide variety of detoxification polymorphisms.

We are beginning to identify what are called the metabolic “yellow canaries,” individuals with a predisposition toward higher sensitivity to certain chemicals as a consequence of altered first-pass detoxification through phase I and phase II. The article “Inheritance and Drug Response” contains a detailed discussion of these genetic polymorphisms, those that are found in the constitutive family of enzymes related to detoxification, such as cytochrome P4502D6, and those found in the inducible family, including cytochrome P4501A2, 1E1, and 1B1. These enzymes can be induced to higher levels of activity

upon exposure to substances. It is the induction of these enzymes that can lead to liver injury through increased oxidative stress.

The companion article is titled “Pharmacogenomics—Drug Disposition, Drug Targets, and Side Effects.” [6] It follows up on the theme and indicates where the field is heading. This is another classic example in functional medicine of the connection between genes and environment. Individuals have unique genetic predispositions related to the polymorphic characteristics of these detoxification enzymes. The expression and activity of these enzymes, however, can be modified through environment, not just by exposure to the drug that needs to be detoxified, but also by exposure to other agents that influence expression of these enzymes and their activity.

Expression of the enzymes includes the expression of phase II conjugases like quinone reductase or glutathione S-transferase, which are known to be induced as a consequence of the consumption of glucosinolate-rich cruciferous vegetables. Consumption of these vegetables affects detoxification ability. Specific nutrients may influence specific subfamilies of cytochrome P450s. It is not simply a matter of eating your vegetables; it is eating the right vegetables to promote appropriate detoxification outcome.

Adverse Drug Reactions and Genetic Variability
We are beginning to examine this extraordinary variability. According to the authors of the article I cited above, “The existence of large population differences with small intra-patient variability is consistent with inheritance as a determinant of drug response; it is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects.”

The ability to metabolize a specific drug can vary by 100-fold from one individual to another. This may be one of the most dramatic variations in human biochemistry. It means that a specific dose of a drug in one person may be metabolized 100 times slower or faster than in another individual given the same milligram-per-body surface area amount of that agent.

Explaining Adverse Drug Reactions
This accounts for the prevalence of adverse drug reactions. We treat all people as average individuals, but there are outliers who may have atypical reactions as either slow or rapid metabolizers. That may explain some of the 106,000 adverse drug reactions that result in death in hospitals each year, according to an article published in 1998in *JAMA*.[7]

This article suggests that these conditions represent between the 4th and 6th leading cause of death in America. They have never even been recognized in the past.

What we do not look for, we often do not find. It comes as a great surprise how many people die in hospitals, not because of the disease that led to their admission, but as a consequence of adverse drug reactions that produced a cataclysmic outcome called death—110,000 possible deaths in 1991, according to these data

Many variables play a role in medicine. In functional medicine we have taken on the responsibility of looking at these variables as we try to develop a system for managing patients. We need to look at their genetic uniquenesses and susceptibilities from a family and personal health history. We need to look at their dietary variables, their lifestyle modifiers, and whether they are carrying chronic infections. All of

those variables influence how those agents are metabolized. We also need to be aware that exogenous environmental chemicals may vie for the same detoxification pathways, as well as endogenous substances. There may be a total load effect. Substances from the body's own biosynthesis, the external environment, gut bacterial metabolism; and OTC or prescription drugs all produce a load on the detoxification system.

Personalized Medicine

Dr. Jay Cohen has spoken a lot about adverse drug reaction. He believes these problems could be reduced if we were to treat each individual according to his or her specific need. This is personalized medicine. Doctors generally use prescription drugs as if all people were the same. That can lead to significant difficulties. In a recent article, Dr. Cohen discusses the potency of different statin drugs, for example, and their relative toxicities, one to the other. [8]He talks about ACE inhibitors, angiotensin inhibitors, beta blockers, calcium antagonists, diuretics, and antihypertensive drugs. He explains the remarkable differences in the way they are metabolized. He advocates using lower, safer effective doses for various medications, which can have a tremendous influence on overall safety.

Dr. Cohen describes all of this subject matter in his book, *Over Dose: The Case against the Drug Companies.*[9] He discusses how to use lower, safer, more effective doses of the 36 most frequently prescribed drugs, and he ties that together with the concepts of pharmacogenomics, diet, lifestyle, and environmental factors.

In speaking about toxicity, we should also consider potential nutrient toxicity. One nutrient that has been in the news recently is retinol, or retinyl compounds like retinyl palmitate or acetate, or vitamin A. The question is whether excess vitamin A can cause hip fracture.

The authors of an article in the *Harvard Women's Health Watch* recently explain that hip fracture is one of the most dreaded risks of aging. More than 350,000 hip fractures occur annually in the United States, mostly in women over the age of 65.[10] Half of these women never regain the ability to live independently, and about 20 percent die within a year. Therefore, hip fracture might be considered a lethal event in some individuals. Fifteen percent of women who are currently 50 years old will have suffered a hip fracture before they reach 80.

Causes of Hip Fracture

What causes hip fracture? We often think it is calcium deficiency, and the person has a bone demineralization. Published epidemiological studies on this topic disagree, however, particularly the work of Walter Willett, which we described last year in *FMU*. He has found that excess vitamin A intake may be another relative risk factor in the problems associated with bone loss or bone fracture. That study, published in the *Journal of the American Medical Association*, found that long-term intake of a diet high in retinol may promote the development of osteoporotic hip fractures in women.[11]

The amount of retinol in fortified foods and vitamin supplements, according to the authors, should be reassessed in light of these data. These investigators found that in looking at 72,337 postmenopausal women from age 34 to 77, the incidence of hip fracture increased significantly when vitamin A intake was greater than 3000 µg per day of retinol equivalent. Are a lot of women who are taking vitamin supplements and eating a quality diet already over the threshold and into the higher risk group, or is the

higher risk group really exaggerated and there may be other factors?

Vitamin A and Risk of Osteoporotic Fractures

Aneditorial in *JAMA* asked if high intake of vitamin A poses a risk for osteoporotic fractures.[12]The author of this editorial was Dr. John Hathcock from the Council for Responsible Nutrition, who was on the Food Nutrition Board that established the RDAs. He pointed out that a number of studies were reviewed in 2001, including the National Health & Nutrition Examination Survey, No. 3, or NHANES III, and a smaller study in Iceland. Review of those studies failed to find any relationship between serum retinyl esters, a marker of excessive retinol intake, and bone mineral density, a marker of bone strength.

A recent double-blind, crossover clinical trial showed that a large single daily dose of 15 mg of retinyl palmitate (providing 8190 µg [27260 IU] of retinol) decreased the serum calcium response to a single dose of the activated form of vitamin D several hours after administration. This study suggested a more complex mechanism for possible adverse effects of massive intakes of retinol on bone health. The issue of vitamin A and bone health is not whether the effect occurs at the usual levels of retinol intake experienced by most persons. Overall, the evidence relating to a possible relationship between moderately high retinol intake and possible adverse effects on bone health remains inconclusive. We are still in the fact-finding realm.

Retinoic Acid and Hip Fractures

In an editorial in the *New England Journal of Medicine*, Dr. Paul Lips talks about retinoic acid, hypervitaminosis A, and fractures.[13] He points out that retinol in the body is converted into retinoic acid, an active metabolite of vitamin A, stimulating osteoclast formation and activity and leading to increased bone resorption and peri-osteo bone formation. Hypercalcemia may also be observed with increased retinoic acid levels. It is important to recall, however, that the body does not indiscriminately convert retinol to retinoic acid. It is a very tightly controlled process. Giving vitamin A itself may not necessarily increase retinoic acid levels, because of its feedback control mechanisms.

A recent article in the *New England Journal of Medicine* is titled “Serum Retinol Levels and the Risk of Fracture.”[14] The authors of this study looked at 2322 men, age 49 to 51, in a population-based, longitudinal cohort study, examining serum retinol and beta-carotene and fractures. They found 266 documented fractures during 30 years of follow-up, and Cox regression analysis appeared to show a correlation between serum retinol levels and fracture incidence. Their findings were consistent with results seen in some animal studies, as well as with Willett’s epidemiological study. The results suggest that current vitamin A level supplementation in food in many Western countries may need to be reassessed and decreased because of the apparent increase in fractures, not only in women, but in men as well.

Finding the Right Dose of Vitamin A

The story is not completely clear. Other papers, such as one that appeared in *Osteoarthritis and Cartilage*, found articular cartilage degradation and a de-differentiation of chondrocytes by producing either vitamin A insufficiency or vitamin A toxicity.[15] By giving too much vitamin A, you can cause the same problem as not having enough. There is a parabolic dose response curve; too much is not good; too little is not good. The difficulty is in finding the ideal, the mid-range.

A recent paper illustrates the principle that what is ideal is related to the genetic uniqueness of the patient and his environmental state. The article, "Short-Term Vitamin A Supplementation Does Not Affect Bone Turnover in Men," is based on a study conducted at the Institute on Aging, University of Wisconsin, Madison.[16] The authors purposely supplemented 80 healthy men, age 18-58 years, with 7576 µg (25000 IU) of retinol palmitate daily. That would be well above the 3000 µg dose we previously described. They measured specific markers for bone loss—serum bone specific alkaline phosphatase and N-Telopeptide of type 1 collagen. They also looked at serum osteocalcin at baseline and after six weeks of supplementation.

Results of Vitamin A Supplementation Study
They found in all three of those measurements of bone status that there was no difference between the placebo group and the group that received the supplemental vitamin A. The authors conclude, "It is unlikely that short-term administration of vitamin A would contribute to the development of osteoporosis. Whether long-term vitamin A supplementation might have adverse skeletal effects remains to be determined."

The last chapter of this story has not been written. We need to look at the range of variability from person to person, what is considered excess, how it comes into balance with other things such as vitamin D and calcium, and the general metabolic status of the patient. It seems prudent not to give vitamin A at high doses without following bone loss markers. If you get above 5000 µg unit of retinol equivalent per day, you should consider following bone loss markers if it is going to be a long-term therapeutic intervention. That way, you are measuring parameters that might reflect bone loss

This discussion concerns biomarkers of nutritional exposure and status. A review article in the *Journal of Nutrition* considers the lab tests we use, how we use them, and how we interpret them to assess nutritional status. This appeared in the edited transcripts of a symposium titled Biomarkers of Nutritional Exposure and Nutritional Status: An Overview." [17]

The question is how to use a lab test. It is related to the beginning of this discussion regarding evaluation of potassium. We should make sure that what we are evaluating is a direct relationship to nutrition. If it is not, we need to determine how the indirect relationship to nutrition status plays out through absorption, distribution, uptake, utilization, and excretion components.

Nutrient Interactions
Each nutrient we might commonly use in nutritional therapy has its unique pharmacogenomics, pharmacogenetics, or kinetics related to the way it is turned over in the body and how it is affected by other factors. For instance, vitamin D is not really a vitamin. We consider it a prohormone that has to be metabolized into 1,25-dehydroxycholecalciferol so it can then serve as a hormonal modulator of gene expression, influencing calcium binding protein, and increasing calcium uptake.

You would not talk about vitamin D by itself. You might talk about kidney function that leads to the 1-hydroxylation and then liver function, at least the 25-hydroxylation, so you get the active metabolite. How is that in balance relative to parathyroid hormone and the calcium/phosphorus ratio of the diet? Is the person getting adequate magnesium? Is he or she getting weight-bearing exercise? What are the other variables that might change intracellular pH to move it toward the acid side? These could be things that produce metabolic acidosis. We need to consider all of these variables when we talk about the adequate

level of vitamin D.

Vitamin K, Antioxidant Protection
Vitamin K plays an important role in osteoclasts, osteoblasts, and embryogenesis, and it is involved in controlling the balance between bone reformation and bone loss. We need to determine if the individual is getting adequate vitamin K in his or her diet.

How do you assess antioxidant protection? One article in this series of papers in the *Journal of Nutrition* on the use of the laboratory for assessing nutritional status specifically considers antioxidant nutrients and the use of biomarkers.[18] The author discusses plasma lipid peroxides as a screening tool, and the use of oxidized DNA as 8-hydroxy-2-'deoxyguanasine to look at the amount of DNA that has been injured by oxidation, and trying to track that back to antioxidant status and free radical oxidative injury. We are just beginning to develop tests to evaluate the status of nutrients. Functional laboratory testing and functional physiology represent an emerging field.

On side II we will take this concept from the high tech to clinical application, with the use of a very simple, nonpolluting, inexpensive, noninvasive treatment good for just about every chronic disease.

INTERVIEW TRANSCRIPT

Side II
Clinician of the Month
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JB: It's time for our Clinician/Researcher of the Month interview. This month's guest is Dr. David Musnick. His contributions include bringing the exercise prescription into medicine. He is co-author of a book that should be on your reading list, titled Conditioning for Outdoor Fitness, published in 1999. 19 Dr. Musnick is an internist who received his training at the University of California, San Francisco Medical School. Thank you for being with us today, David. I appreciate your giving us this time to help our listeners understand the role of exercise and conditioning in 21st century functional medicine.

Exercise for All Patients?
DM: You're welcome. I'm glad to be here.

JB: We often hear the term "exercise prescription," which conjures up a mental model of a prescription pad with dumbbells or a running track. What is meant by the term exercise prescription, and is it an important part of what every practitioner should be providing for patients in evaluating them and drawing up treatment plans?

DM: If a patient is to achieve the benefits of exercise, the physician needs to be trained and skilled in exercise prescription. An exercise prescription is an individualized prescription for a patient, outlining aerobic exercise, strength training, balance training, and possibly flexibility training, appropriate for that patient's condition. The aerobic exercise prescription is the most important element a physician can give because it has been studied so extensively in regard to numerous cardiovascular and other health benefits.

To write a prescription, a physician has to design a specific program for a patient. In regard to aerobic exercise, the prescription must include the variables of the exercise, including intensity, duration, and frequency. He or she must then give choices to the patient for possible modes of exercise so the patient will be successful and it will not result in a flair-up of any preexisting musculoskeletal conditions. It also has to be documented on a form that the doctor can monitor. I recommend specific forms, monitoring devices, for the physician to write up the initial exercise prescription, and to modify it as the patient returns for follow-up visits, using appropriate forms to achieve success and the benefits the physician wants.

Getting Patients Involved in Exercise

JB: At the Comprehensive Medicine Clinic, your present facility in Bellevue, Washington, do patients come in looking for an exercise prescription? Or do you have to introduce them to the subject and engage them in a discussion of exercise?

DM: The vast majority of my patients do not think I'm going to give them an exercise prescription, although if they find out I wrote a book on the subject, they might assume that might be part of the plan. I see patients for a variety of problems, and I incorporate an exercise prescription into almost all of them. If a patient comes in for an annual physical, my physical is a much more detailed preventive type of evaluation than the average one. I take a complex, detailed exercise history and outline goals for my patient. Then I design an exercise program or modify the present one to better meet the goals the patient and I have for his or her health.

I use exercise prescription for stroke prevention, cardiovascular risk reduction, cancer prevention, and for patients with any neurodegenerative disorder. For patients who have sarcopenia with balance dysfunction, I integrate a balance proprioceptive exercise prescription. Because there is such a benefit from exercise, I use strength training, balance training, aerobic training, or flexibility training in the vast majority of patients.

Cardiovascular, Hypertensive, and Syndrome X Benefits of Exercise

JB: Let's discuss the specific benefits of exercise in relation to the big three areas you mentioned. I would like to treat them as separate topics. First might be the cardiovascular connection; second, the hypertensive connection, which obviously interrelates with the cardiovascular condition; and third is syndrome X, or an insulin resistance condition. All three of those are interrelated, but they all have slightly different nuances. Let's start with the cardiovascular area and cholesterol screening. How do you evaluate it, and what expectations might you have with the appropriately implemented exercise prescription?

DM: I think it's appropriate to outline what the cardiovascular benefits are from the aerobic exercise prescription, and how to modify it. The actual risk for myocardial infarction and myocardial mortality is significantly reduced if a person engages in five to six days a week of 30 minutes of aerobic exercise in what we call the training heart rate zone.

If the patient is on a beta blocker or a calcium channel blocker, that prescription has to be modified because it wouldn't be adjusted to the training heart rate zone. A physician might want a patient to decrease a significant risk in cardiovascular mortality and the development of coronary artery disease, which might include a reduction in LDL and an increase in HDL.

Research over the past several years has demonstrated that aerobic exercise, done in the right frequency, duration, and intensity, can decrease C-reactive protein and thus decrease systemic inflammation. The effects of that program will be a decrease in cardiovascular risk and in cerebral vascular disease. An aerobic exercise prescription can be used to decrease the risk of myocardial infarction, the extensiveness of coronary artery disease, and the incidence of stroke, as well as bringing the blood pressure down and modifying the cholesterol factors.

Analytes in Cardiovascular Screening

JB: There has been considerable discussion of the cost effectiveness of using some of the analytes in cardiovascular screening, such as fibrinogen, C-reactive protein, or lipoprotein a or b, the so-called subfractions of cholesterol. Do you find value in using some of these more esoteric analytes?

DM: Yes, although I find that some of the most important variables to analyze will be related to exercise and some of them will not. It is extremely important to measure high sensitivity C-reactive protein. That will come down within even six to eight weeks on an aerobic exercise program. HDL will usually rise within two to four weeks on an aerobic exercise program; LDL will start coming down.

Homocysteine doesn't seem to respond to aerobic exercise, although I think it's an extremely important variable that I monitor in my patients. Fibrinogen, from the studies, does not seem to be modified much from an aerobic exercise program. I check it for other reasons, but I don't monitor that variable in terms of seeing the effectiveness of an aerobic exercise program. The most significant monitoring parameters, in terms of cardiovascular and cerebral vascular disease, are LDL, HDL, and C-reactive protein. Lipoprotein a does not seem to respond that much to aerobic exercise, at least in the studies that are presently out there.

Benefits of Exercise

JB: Do some people ask if you consider exercise a primary or a secondary treatment for cardiovascular risk? Some people say exercise is only associated with improvement in lean body mass, so exercise is just a way to lose weight and improve body mass index (BMI). From what I understand, the benefits of exercise extend well beyond improving BMI.

DM: Absolutely. Numerous studies have tried to control for BMI and obesity. They show separate effects from aerobic exercise other than just the effect on improving BMI.

Exercise and hypertension

JB: Let's move to a closely associated condition—hypertension. In some seminars, I've heard doctors say that resistance exercise will only increase your blood pressure so you should never put a person with hypertension on a resistance exercise program. What is myth and what is fact in relation to the appropriate kind of exercise in the hypertensive patient?

DM: I believe aerobic exercise is essential for treating the hypertensive patient. Resistance exercise can also be used in the hypertensive patient. Clinicians need to know that when a patient is lifting weights and performing a Valsalva maneuver, the blood pressure can go quite high in a hypertensive patient. We don't want such people doing what we call isometric exercise or exercise with low repetitions with a lot of resistance. That being said, a strength training program to improve lean body mass can easily be prescribed for any hypertensive patient, unless the patient has malignant hypertension.

In regard to the aerobic exercise component of that program, it appears we can lower systolic blood pressure approximately 10 points and diastolic about 7 to 8 points, and sometimes even more than that. The studies document that type of lowering within four to six weeks of an aerobic exercise program. There is an effect immediately after aerobic exercise whereby the blood pressure will be lowered almost immediately after the cessation of the aerobic exercise program. During aerobic exercise, the blood pressure increases with regard to the intensity of the exercise. I feel that aerobic exercise is an essential part of managing any hypertensive patient to lower blood pressure. If you are trying to do this with lifestyle changes, the exercise program is essential.

Diet and Exercise

JB: When we think of hypertension, we often think about dietary approaches to treat it. The Dash Study, for example, showed dramatic benefit in lowering both systolic and diastolic blood pressure by moving people away from a diet high in refined white sugar, flour, and fat into a diet higher in whole grains and fruits and vegetables, and magnesium- and potassium-rich foods. Have you had experience in looking at the combination of exercise and dietary modification? Does the combination provide additional benefit, or do you get the majority of benefit from exercise alone?

DM: Iusually do a combined approach using diet, supplements, and exercise at the same time, but sometimes I manipulate one variable or another, depending on what the patient is already doing. I see the most benefit when I have them on a healthy diet. I usually don’t use a higher carbohydrate diet; I usually use a lower-carbohydrate diet.

The other thing that is probably going on with regard to hypertensive patients is when you use an exercise program effectively, the blood pressure will decline for a number of different reasons. Oftentimes body fat gradually decreases as well. There will be a reduction related to actual benefit from the aerobic exercise and then gradually there will be even more benefit from a few things—the reduction in adipose tissue and BMI—but also stress reduction.

I have observed reductions in systolic blood pressure that I couldn’t account for in patients, with regard to the studies stating that the maximum reduction is 10 points systolic. I’ve had numerous patients with systolic blood pressures as high as 160 or 170, and I was able to control their blood pressure with the combination program I’ve outlined (as long as they were compliant with the exercise). Their systolic pressure came down to 140, a much more significant decrease than that predicted by the studies that have been done.

Insulin Resistance and Exercise

JB: This talk about hypertension and diet leads into what Gerald Reaven described as the triad associated with syndrome X. Clearly, insulin resistance also plays a role. We should probably segue into discussing insulin resistance and the exercise prescription, and how you integrate that in your treatment programs. Have you had success with insulin sensitivity?

DM: Absolutely. I’ve treated hundreds of patients with insulin resistance syndrome, anywhere from a patient who comes in with a medication to manage each variable, to a patient who is just developing syndrome X.

Aerobic exercise increases insulin sensitivity. Aerobic exercise in the syndrome X patient should be

designed in a particular way. A lot of these patients are obese, so I might have them begin an aerobic exercise program with 15 minutes of stationary cycling, because they might flare up their knees or develop tendonitis just with walking. I let them begin with stationary cycling, or choose a modality they are willing to do, gradually increasing the program by 1 minute until we're up to 45 minutes of aerobic exercise five to six days a week. The reason is that after 20 minutes, more fat is selectively burned, so the patient has a higher chance of weight loss if he or she exercises longer than the 30 minutes that's usually recommended.

Exercise Intensity

We also want them doing lower intensity exercise. We want them training at 60 to 70 percent, or slightly less than 70 percent of their maximum predicted or measured heart rate. This is different from the program for patients with hypertension and other conditions that don't include syndrome X, where we want them at 70 to 80 percent of their maximum heart rate. We want syndrome X patients to exercise at lower heart rates for longer duration, to burn more fat, and have more effect on their blood sugar.

Decreasing Medications

What we usually see over time is that if they start out on medications to lower their glucose, you can gradually decrease the medications, because if you're combining exercise with chromium and/or some other functional medicine interventions, the patient's blood sugar is going to decline fairly rapidly. We want to keep closer track of them.

Also, the blood pressure will start coming down. If they're on a blood pressure medication, often it can be decreased or they can be taken off of it. When they start losing weight, they have even more significant lowering of their blood pressure. They also have lowering of their total cholesterol and their LDL. Most of these people have a very significant lowering of their triglycerides and increases in their HDL; studies have shown that patients who seem to raise their HDL more with aerobic exercise are those who start out with higher triglycerides in the first place.

Insulin Resistance in Non-Obese Patients

JB: Some insulin-resistant or syndrome X patients may not be obese or even overweight. Does the exercise prescription have the same impact on improving their insulin sensitivity as it has on those with a higher BMI?

DM: Yes, but I'd modify the prescription slightly. The exercise prescription would then be in what I would call the minimum health benefit prescription. That would be 30 minutes in the target heart rate zone four, five, or six days a week for the purpose of improving insulin sensitivity, decreasing total cholesterol and LDL, for improving HDL, and for decreasing C-reactive protein. In other words, it would be a prescription for improving insulin resistance and giving them the cardiovascular health benefits. We wouldn't want them doing the longer duration exercise because we're not that interested in weight loss in those cases.

Insulin Resistance and Obesity

JB: In most cases, we are led to believe, insulin resistance is a consequence of weight gain (i.e., obesity causes insulin resistance). Clinically, however, one observes people without a BMI problem whose insulin sensitivity improves with exercise. What is the explanation? Can we say insulin resistance only has an obesity component to it, or that insulin resistance causes obesity? What is your opinion as you look

at these patients?

DM: I would say the vast majority of insulin-resistant patients are significantly overweight. A certain percentage of these patients are not, however, so we'd have to say it's a multifactorial issue. With regard to patients who are insulin resistant but do not gain weight or become overweight, we'd have to say multiple factors led to their insulin resistance. Therefore, exercise, which improves insulin sensitivity, is indicated in these patients for the goal of improving their insulin sensitivity.

Endocrine Effects of Exercise

JB: I recently read a book on fertility and body composition in women. This book, which is well written and documented, makes the point that there is an association between body fatness and fertility in women. At both ends of the parabolic curve, either at high body fatness, or at low body fatness, women have a very high prevalence of infertility. It is this author's contention that the weight issue is polarized among women. A lot of them now have a BMI that is too high, and a lot of them have a BMI that is too low. The consequence is an adverse endocrinological impact on reproduction in both groups. Have you seen women whose endocrine systems have been adversely influenced by an exercise program or needs to be modified?

DM: The issue of BMI in females is interesting because you could have a woman who's doing aerobic exercise, developing the over-training syndrome, and developing hormone abnormalities. Amenorrhea can lead to infertility. The majority of women I've seen who are insulin-resistant are overweight and have a problem with BMI. Aerobic exercise is a good idea, but I would not want women who are trying to become pregnant to lose too much body fat. I would want to monitor them endocrinologically as well to make sure they're not developing amenorrhea syndrome and/or low estrogen states.

Exercise Compliance

JB: A lot of good clinical science supports the value of people getting into the appropriate exercise prescription as part of their therapy. Regardless of how good it is for them, it is like getting some people to eat broccoli or Brussels sprouts. How do you get them to comply?

DM: That's an important question. First, prescribing exercise, monitoring it, and getting compliance is a skill. It's not taught in medical school, and in general it's not taught in residencies. I teach the naturopathic students at Bastyr University. I also teach at the University of Washington Medical Center, Department of Orthopedics and Sports Medicine. In general, however, it isn't taught in most medical schools. Clinicians actually have to learn it in practice.

Agreeing on Benefits of Exercise

Let me outline what I've found is involved. First, we need to educate patients to inform them of the benefits involved in the program of exercise we're recommending, whether it's strength training, balance training, or aerobic exercise. Patients have to agree they want those benefits. Most of the time, the benefits the physician wants are going to be similar to those the patient wants, but sometimes the patient wants additional benefits such as more weight loss or more stress reduction. Patients have to agree on the benefits they want, and they have to understand that in order to get those benefits, they have to participate. That's number one.

Individualized Exercise Program

Second, we need to design an individual exercise program for that patient so he or she will be likely to carry it out. This involves determining the patient's musculoskeletal conditions and restrictions. The patient will be given a program (for instance, the aerobic exercise part) that will not flare up a preexisting joint problem. If a patient develops tendonitis, bursitis, or a joint problem from exercise, he or she is going to be less likely to continue doing it.

Monitoring Progress

Another thing is a monitoring device. We need to be able to monitor patients so when they come back, we can see what they've actually been doing. The most important things to monitor are the activities they have been doing, how many minutes they have been doing them, and what their training heart rate or gradient of perceived exertion has been. I've developed a monitoring device form I use with my patients. I'm going to be teaching a workshop on using that form in Tucson at the IFM Symposium in May.

I have found that prior to using a monitoring device, I wasn't getting good compliance. When the patient brings this form in, I can look at a whole month. (There's a calendar on the monitoring device form.) I can see, for example, that on Monday, Tuesday, Thursday, and Friday they exercised for 30 minutes, their heart rate was 125, and they recorded any symptoms they had. I can see whether we're getting compliance or not.

Trouble

It is also most important to be able to trouble-shoot problems with compliance. Believe it or not, helping patients manage their time and schedule their exercise, and figuring out the obstacles to doing that, is one of the most important things a physician can do in gaining compliance.

In summary, we educate the patient about the benefits. We have them circle the benefits they want to achieve on the monitoring form, and we advise them to put the form in a readily accessible place in their home (on the bathroom mirror, for instance). Patients also sign a little commitment statement that they've agreed to do the exercise to achieve these benefits. We bring the patient back for a visit within two to three weeks of prescribing the exercise to troubleshoot any roadblocks, which usually develop within two to three weeks.

Validation and Progress

We validate patients for the exercise they are doing and help them make progress. We also make the prescription progressive. Usually, the prescription needs to be modified at the second visit. Oftentimes, we bring patients back to go over laboratory results, diet, supplements, and whatever else we're following. Then we do some monitoring.

I recommend within six to eight weeks of the patient being on the full program, that physicians do some laboratory testing if they're following HDL, LDL, C-reactive protein, hemoglobin A1C, and/or fasting blood sugar. Then it's reasonable to do some monitoring. You can also show the patient with those lab tests that they're improving, besides doing BMI measurements and recording weight changes.

Third Party Reimbursement

JB: I know you will go over this in detail in your workshop at the 10th Annual Symposium on Functional Medicine. Tapes from your workshop will also be available for those who want to followup.

Since you obviously spend time with patients in going through this exercise prescription, and it wasn't taught in medical schools and is not a standard thing that everybody does, is there a way of being reimbursed for services? Does your office staff handle that? How does it work in practice?

DM: If a clinician is billing an insurance company, there are particular codes for kinetic activities. There's a code for therapeutic exercise. This would be considered health counseling, and physicians can bill for that. It's really important to document it in the chart—the educational counseling done regarding exercise, the amount of time spent with the patient, and billing these particular codes, or the regular codes for the amount of time you're spending with a patient, which might be a 99214.

The other thing I think is important is to do balance and proprioception testing on patients and to document that. The physician can teach balance exercise, the space on the balance tests they're doing, and indicate that as therapeutic exercise or kinetic activities. If we prevent hip fractures in perimenopausal patients or those with osteoporosis, we can also prevent the DVTs and other serious complications. Taking some time to check balance and rehab balance, and documenting it means physicians can bill for that as well. That's an important part of the exercise prescription.

Clinical Relevance
JB: Dr. Musnick, thank you. This is the most comprehensive discussion we've had about exercise in the practice of medicine. You have given us a lot of clinically useful information. There will be a lot more, I'm sure, to learn from your workshop. Thanks for reminding us that some health benefits that don't come in bottles are the most powerful techniques we have in all of medicine.

The concept of nutritional status using the laboratory is no small issue, and one I know is of great interest to our listeners. How do we appropriately use various laboratory tests to assess everything from antioxidant status to vitamin E to essential fatty acids to protein sufficiency, to essential amino acids, and even conditionally essential nutrients? That will be the leadoff discussion in the June issue of FMU.

Estrogen and Breast Cancer
How do we modulate pharmacogenomic uniqueness relative to detoxification using diet intervention? A recent editorial in the *Journal of the National Cancer Institute*, titled "Estrogen and DNA Damage: The Silent Source of Breast Cancer?" addresses this problem.[20] According to the author, the way estrogen is metabolized to 4-hydroxy or catecholestrogen metabolites may have something to do with its relative carcinogenicity or toxicity. Studies of these interrelationships are being conducted at the University of Nebraska Medical Center by Cavalieri and Rogan; Joachim Liehr, a cancer researcher at the Stehlin Foundation for Cancer Research in Houston; Dr. James Yager of Johns Hopkins University; and Dr. Fritz Parl. All of these investigators are looking at 4-hydroxylation patterns and their subsequent methylation, and how that influences relative risk to breast cancer.

The production of the 4-hydroxylated estrogens occurs in the breast as a consequence of the activity of a specific cytochrome P450, 1B1, which can be downregulated because it is an inducible and suppressed potential enzyme, through dietary intervention. Certain phytonutrients are known to downregulate cytochrome P4501B1. With some enzymes, we might want to use dietary factors to upregulate, and with others we might want to downregulate, depending on the personality of the biotransformed endproducts. For example, isoflavones in kudzu are known to lower the expression of cytochrome P4501B1. Kudzu isoflavones may have a preferable effect in lowering the risk of breast cancer due to the formation of

these 4-hydroxylated estrogens.

Selenium and Prevention of Cancer
There is also increasing evidence that selenium plays an important role in preventing various forms of cancer due to its impact on detoxification. It activates and supports an enzyme called glutathione S-transferase, or GSH transferase and GSH peroxidase. It supports an enzyme called glutathione peroxidase (GSH peroxidase), the coupled enzyme with glutathione transferase. Glutathione peroxidase requires selenium for its activity, and low selenium status can compromise the ability of GSH peroxidase to do its work. As a consequence, it can lower glutathione availability for conjugation and detoxification and render that person more susceptible to oxidative injury.

This is the topic of an article in the *Journal of the National Cancer Institute,* titled "Selenium for Prevention: Eating Your Way to Better DNA Repair?"[21] Selenium helps lower oxidative injury. A number of studies have followed up on the early observation that 200 µg of selenium a day had a positive role in reducing overall risk to cancer.

Dietary Isothiocyanates and Colorectal Cancer Risk
Dietary isothiocyanates can influence glutathione S-transferase activity and have been demonstrated to lower colorectal cancer risk. This is the topic of a study recently published in*Carcinogenesis.*[22] The authors indicate that gene/diet interaction may be important in evaluating the effect of risk-enhancing compounds in the colorectum or their limitation of risk by upregulating expression of detoxification enzymes.

We often assume detoxification occurs solely in the liver. Considerable detoxification also occurs in the gastrointestinal mucosa, however, and that detoxification requires a certain level of these nutrients for its activity.

Modulation of Inflammatory Mediators with Omega 3 Fatty Acids
A last example of the use of a laboratory and nutritional intervention concerns modulation of inflammatory mediators through omega 3 fatty acids. Red cell plasma fatty acid levels can be helpful for evaluating the relative ratio of omega 6 proinflammatory precursors like arachidonic acid, and omega 3 antinflammatory precursors like docosahexaenoic (DHA) or eicosapentaenoic (EPA) acids. This is the ratio of omega 6 to omega 3 fatty acids. Recently, people have been asking how the omega 3 fatty acids actually help lower the risk of disorders like cardiovascular disease. It would seem that feeding fat to people would only increase their heart disease risk, but studies indicate the risk declines when the omega 3 fats are increased.

An article in a recent issue of the *Lancet* is titled "Association of n-3 Polyunsaturated Fatty Acids with Stability of Atherosclerotic Plaques: A Randomised Controlled Trial."[23] The thought has emerged over the last few years that heart disease risk is not a consequence of the plaque itself, or what we might call a cardiovascular event. That risk depends more on the stability of the plaque.

Plaque Stability
If the plaque breaks off and is associated with a thrombotic event, the result may be a life-threatening myocardial event. But if the plaque is stable and allows blood flow to be collateralized around it, the

relative risk of a major coronary event is significantly reduced. This *Lancet* study is the first trial I have seen that looked at 188 patients who were enrolled and randomized (18 withdrew and eight were excluded) and stayed on the program for a median of 42 days.

The investigators examined carotid plaque formation after the role of EPA/DHA supplementation versus placebo. They found a significant influence on plaque formation and plaque stability when the individual was supplemented for just a little over a month with omega 3 fatty acids versus getting sunflower oil, linoleic acid, or omega 6 supplementation (sunflower oil). The relative amount of supplementation was not extraordinary. It was only 6 grams per day. Omega 3 fatty acids appear to play an interesting role, not only in the prevention of plaque, but in the stability of plaque. In fact, the interpretation of this study is that atherosclerotic plaques readily incorporate n-3 fatty acids from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of n-6 fatty acids does not affect carotid plaque fatty-acid composition or stability over the period of time studied.

The authors conclude the stability of plaques could explain reductions in non-fatal and fatal cardiovascular events associated with increased n-3 fatty acid intake. The conclusion we can draw is to eat cold-water fish, making sure it is mercury-free.

Fish Oil Consumption and Arterial Disease

Another study with a similar conclusion appeared in the *Journal of Nutrition.* It is titled “Fish Oil Consumption and Reduction of Arterial Disease.”[24] Investigators found fish oil consumption helped normalize the prethrombotic state and reduced arterial disease at fairly modest levels of intake—3 to 6 grams a day. They looked at controls versus individuals who received the omega 3 fatty acids from fish oil and found the possibility that the dietary effect on hemostatic and lipid factors involves transcription regulation of multiple genes, perhaps in a subject-dependent manner.

What this means is that fatty acids of the omega 3 family speak to the genes. Omega 3 fatty acids have receptor sites in the so-called orphan nuclear receptor super-family of gene regulatory factors that control the expression of specific genes. These genes could obviously be expressed in different levels in different individuals based on their single nucleotide polymorphisms (SNPs), so we might see a variable effect.

Not everyone responds to omega 3 fatty acids in the same way. Downregulating inflammatory gene expression and upregulating processes associated with arterial dynamics, proper immune system function, and lowered conversion of macrophages to foam cells reduces atherogenic risk. It also affects plaque formation and stability.

Fatty Acids in IBD

That might also hold true for fatty acids in inflammatory disorders like inflammatory bowel disease (IBD). A paper in the journal *Lipids* showed that fatty acid supplements of omega 3 fatty acids directly into the small bowel, had a remarkable influence on reducing disease activity in the bowel in individuals with IBD.[25] Dosage of the omega 3 fatty acid supplements was 5 to 6 grams per day.

Flax Seed Oil

Finally, we might wonder if giving a patient flax seed oil is the same as giving fish oil. The authors of a recent paper in the *American Journal of Clinical Nutrition* showed that if you supplement lactating

women with flax seed oil as a source of alpha linolenic acid, ALA, you do not increase their breast milk DHA levels.[26] It suggests that the conversion of ALA, which is flax oil fatty acid, into DHA may not be very facile in these individuals. If you want to do omega 3 fatty acid therapy for plaque and inflammation, it appears preferable to use the preformed chain-elongated desaturated DHA.

I hope these are some interesting clinical takeaways. We look forward to being with you in June to talk about laboratory assessment in nutritional medicine.

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