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Aunt Cathy's Guide to:

Thinking About OTHER Nutrition Issues in Diabetes

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Introduction:

Blood sugar control is the key focus of nutrition and diet planning for people with diabetes. Historically the most attention has been paid to adjusting the intake of the types and amounts of carbohydrate throughout the day, including the newer concepts of "carbohydrate counting" and the "glycemic index." Additional attention has been paid to total calories and total fat content, plus the content of saturated fat and "trans" fat because of the importance of weight control in diabetes, and the increased risk of cardiovascular disease. **These remain the basis of diet and nutrition interventions for diabetes.**

However, information is becoming available about the special roles of **certain vitamins, minerals, phytochemicals, and some forms of dietary fat** that appear to be useful in various ways in fighting diabetes and its consequences. The nutrition tools described here do not "cure" diabetes – but in many cases they have been shown to have the capacity to **decrease the risk of diabetes developing**. Others have demonstrated that they can be useful for people who already have it by **helping with diabetic control,** or by **making diabetes hurt them less.** This includes reduction in complications like blindness, kidney failure, neuropathy, impaired circulation, and even birth defects.

Some have been shown to be helpful in at least one of seven ways:

1) Enhancing insulin sensitivity.

2) Using antioxidants to minimize secondary damage from poor diabetes control caused by higher than normal production of free radicals.

3) Reducing the severity of inflammation that has been shown to be associated with diabetes to decrease risk of developing diabetes (including Type I, Type II and gestational forms.)

4) Helping stabilize/improve excessive fluctuations of blood sugar that can sometimes be a problem in spite of following the diet very carefully (e.g. what some people refer to as "brittle" diabetes.)

5) Minimizing risk of developing other threats to health and well-being, including conditions that are known to be exacerbated by diabetes.

6) Minimizing the risk of <u>developing</u> diabetes.

7) Discovering the emerging miscellaneous effects of a variety of phytochemicals (plant substances) on the diabetic state.

Happily, all of the diet or nutrient ideas suggested here are also reported to be beneficial for most folks in terms of decreasing risks associated with one or more of a variety of chronic illnesses, including cardiovascular disease, cancer, MS, arthritis (both rheumatoid and osteo,) alzheimers, parkinsonism, depression and osteoporosis.

It is also extremely important to note that all of the suggestions are based on research reported in the legitimate peer-reviewed scientific literature. None are based on wild claims made on the internet (or elsewhere.) There is no law against fiction in America, and therefore there are quite a lot of false claims made for diet and nutrition in particular, often in the interest of selling products. Many of the "dietary supplements" sold are in fact not related to nutrition at all. Many are actually pharmaceutical products, but a loop-hole in the FDA laws allows the marketing substances in the "dietary supplement" category without having to show "safety and effectiveness" as they would if marketed as pharmaceutical products.

Understandably, the existence of so much nutritional quackery in the world has made health professionals hesitant to consider nutrition manipulations to be legitimate adjuncts to management of complex diseases like diabetes. There is a tendency to simply "throw the baby out with the bathwater." The purpose of this paper is simply to highlight areas of research that are identifying the real "babies" to watch out for.

All the suggestions included here are generally regarded as safe at this time (I <u>never</u> recommend anything that comes anywhere near to "scary,") and they are often easy to do and inexpensive. In two cases, the amount of the substance that has been shown to be beneficial is somewhat impractical to attempt when using the currently available over-the-counter products. In these cases, a prescription for the appropriate higher dosage product makes it much simpler. Although these two products and one other are also among the more expensive interventions discussed, the prescription form may be covered by insurance even though the over-the-counter form is not.

As always, the information provided here is simply my best interpretation of the research currently available. No claims are made that any of the large official health organizations have approved this message. It is all subject to change, which is why my papers are clearly marked with a date. And as is always the case for everything in the world "more research is ALWAYS needed," but now there is actually quite a lot of research out there, and certainly for some things there is clearly enough evidence to initiate some safe and cheap changes. It's at the **"won't hurt / really might help"** level.

I am not selling anything – no supplements, no diet plan, no books. My only goal is to try to do some good for people. However, also as always, not all the suggestions are appropriate for every individual, so be sure to **discuss things with your personal health care provider. Feel free to share these materials with him/her.**

In the interests of brevity and saving trees, I will sometimes refer you to another of my papers for more complete information about a particular topic. In addition, papers with more details on this topic and others are available on the website of MeritCare Medical Center:

www.meritcare.com Enter my name in the search box, and then select the option that says "Cathy Breedon's Handouts"

Part One: Enhancing insulin sensitivity

Magnesium and chromium are two minerals which have specific roles in carbohydrate metabolism. **Both are frequently suboptimal in the diets of many Americans** (NHANES) for a variety of reasons and **assuring adequacy** has been shown to be critical for insulin sensitivity. For more details, references, and specific recommendations, please see "Aunt Cathy's Guide to Nutrition: Magnesium" and "Aunt Cathy's Guide to Nutrition: Chromium."

Chromium is a component of "Glucose Tolerance Factor," and it has roles in the metabolism of carbohydrate, protein and fat. Supplementation of chromium picolinate (a well-absorbed form) has recently been shown to be helpful in blood sugar control and weight loss among people with Type II diabetes on sulfonylurea medication However, it may not show the same benefit among obese people on insulin whose type 2 diabetes is poorly controlled. (Diabetes Care. 2006 Mar;29(3):521-5.) In other words, it is not the only player on the team, but it is definitely one of them. It has roles in cholesterol and triglyceride metabolism, heart disease and possibly atypical depression. A review of the literature was just published on this topic: "Clinical studies on chromium picolinate supplementation in diabetes mellitus--a review." **(Chromium references are too many to put in the text, so they follow at the end of this paper.)**

Magnesium has many roles in metabolizing carbohydrate, protein and fat, including being an essential cofactor in the production of ATP via the TCA Cycle. **It is specifically important for the functioning of the insulin receptors on cells**, so magnesium inadequacy is a known contributor to insulin resistance. In a very large prospective study from Harvard it was found that women with the poorest magnesium intake from food compared with the highest were 25% less likely to have developed diabetes over a 16 year period. Magnesium intake has been associated with insulin sensitivity in a threshold fashion, with a threshold at 325 mg magnesium daily. A low magnesium level in the blood (hypomagnesemia) is highly prevalent in diabetic outpatients. High plasma triglycerides, waist circumference and albuminuria are independent correlates of hypomagnesemia. The finding in the National Nutrition and Health Examination Survey (NHANES) that the majority of Americans take in less than 2/3 of the normally recommended amount suggests that improving magnesium

intake has the potential to be helpful in controlling the rapid increase in obesity and type 2 diabetes.

Interestingly, when blood sugars are high enough to **spill over into the urine**, it takes magnesium with it, resulting in an **additional loss of magnesium**. This also occurs when one uses blood pressure medications like **thiazide diuretics**. The diuretics that result in potassium loss will also result in a magnesium loss, but often this is not recognized and corrected. More will be said about magnesium later, and I also have a separate handout available with much more detail on this critical nutrient. **(Magnesium references are too many to put in the text, so they follow at the end of this paper.)**

Recent studies suggest that **vitamin K adequacy** may also have a role in both body fat and diabetes/glucose metabolism. As vitamin K inadequacy is now known to be much more common than was previously believed, the role of vitamin K in diabetes and obesity will likely begin to be evaluated more closely in the scientific community. Phylloquinone intake, insulin sensitivity, and glycemic status in men and women. Am J Clin Nutr. 2008 Jul;88(1):210-5. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007 Aug 10;130(3):456-69. (For more information please see my handout on the meritcare.com website for more on vitamin K: "Aunt Cathy's Guide to: Vitamin K -- New Issues in Cardiovascular Health, Osteoporosis, Cancer of the Liver and Colon, Diabetes and Varicose Veins.")

Exercise also has the capacity of helping to move glucose into the cells, so it is a cornerstone of prevention and also of treatment of Type II diabetes. The mineral **selenium** also appears to assist with this activity along with other functions. It is involved in the thyroid gland insetting one's resting metabolic rate, and it is also a part of a very important antioxidant in the body called glutathione peroxidase. More will be said about selenium later. **(Selenium references and Exercise references are too many to put in the text, so they follow at the end of this paper.)**

Part Two: Minimizing secondary damage from poor diabetes control caused by higher than normal production of free radicals

A greater production of free radicals is well known and documented among people with diabetes (as well as in many other diseases with disturbed metabolism,) with the greatest production in diabetes occurring in the people with the least well-controlled blood sugar levels. Excessive production of free radicals causes serious injury to cells and tissues.

- There is evidence of **significant slowing of the development of diabetes complications by assuring a generous intake of antioxidants.** "Generous" in this context usually means substantially more than the usual RDA-type levels. The RDA guidelines are designed to meet the needs of the "healthy" population, and they have little to say about the specific needs of people with serious metabolic diseases.

- Antioxidants studied quite a lot have included **vitamins C and E, the mineral selenium** (part of the important antioxidant "glutathione peroxidase") **and a variety of carotenoid plant pigments such as lycopene in tomatoes, lutein in spinach and anthocyanin, the blue/red color in blueberries.** The latter substances have been found to be very potent

antioxidants – some at 200 times the antioxidant potential of vitamin E. The ideal level of antioxidant vitamins is unlikely to be around the RDA levels. For example, the author of a recent study concluded that "The results suggest that megadose vitamin C supplementation [1-3mg/day] may have a beneficial effect in diabetes mellitus patients on both glycemic control and antioxidant status. Thus dietary measures to increase plasma vitamin C may be an important health strategy for reducing the complications of diabetic patients." For a review, references and recommendations for these vitamins, minerals and the carotenoid antioxidants, please see "Aunt Cathy's Guide to Eye Health." Other plant substances being explored for diabetes-related effects will be discussed later.

- Higher vitamin C levels in the blood, and fruit and vegetable consumption were recently reported to be related to decreased incidence of type II diabetes in a 12 year study of over 20,000 people. They found a strong inverse association between plasma vitamin C level and diabetes risk. The odds ratio of diabetes in the top quintile of plasma vitamin C was 0.38 in a model adjusted for demographic, lifestyle, and anthropometric variables. In a similarly adjusted model, the odds ratio of diabetes in the top quintile of fruit and vegetable consumption was 0.78. They concluded that higher plasma vitamin C level and, to a lesser degree, fruit and vegetable intake were associated with a substantially decreased risk of diabetes. [Plasma vitamin C level, fruit and vegetable consumption, and the risk of new-onset type 2 diabetes mellitus: the European prospective investigation of cancer--Norfolk prospective study. Arch Intern Med. 2008 Jul 28;168(14):1493-9.]

- Our old friend vitamin E (alpha-tocopherol and it's cousins like gamma-tocopherol) are back in the news with a lot of new research into it's potential to protect against a variety of diabetes related complications. Just between January and July 2008 there has been a huge number of reports that are quite consistent. For example:

Protective effect of stobadine on NCV in streptozotocin-diabetic rats: augmentation by vitamin E. Gen Physiol Biophys. 2008 Jun; 27(2):106-14.Blood antioxidant defense system and dietary survey of elderly diabetic men. Arch Gerontol Geriatr. 1999 Jan-Feb; 28(1):65-83. Correction of HDL dysfunction in individuals with Diabetes and the Haptoglobin 2-2 genotype. Diabetes. 2008 Jul 3. Nutrition impacts the prevalence of peripheral arterial disease in the United States. J Vasc Surg. 2008 Jun 27.HISS-dependent insulin resistance (HDIR) in aged rats is associated with adiposity, progresses to syndrome X, and is attenuated by a unique antioxidant cocktail. Exp Gerontol. 2008 Aug;43(8):790-800. Food selection based on total antioxidant capacity can modify antioxidant intake, systemic inflammation, and liver function without altering markers of oxidative stress. Am J Clin Nutr. 2008 May;87(5):1290-7. Evaluation of the effect of oxidative stress and vitamin E supplementation on renal function in rats with streptozotocin-induced Type 1 diabetes. J Diabetes Complications. 2008 Apr 22. Influence of vitamin E supplementation on endothelial complications in type 2 diabetes mellitus patients who underwent coronary artery bypass graft. J Diabetes Complications. 2008. Cardioprotective effect of vitamin E: rescues of diabetes-induced cardiac malfunction, oxidative stress, and apoptosis in rat. J Diabetes Complications. 2008 Apr 2. Cardioprotective effect of vitamin E: rescues of diabetes-induced cardiac malfunction, oxidative stress, and apoptosis in rat. J Diabetes Complications. 2008 Apr 2The effect of hemodialysis on accelerated atherosclerosis in diabetic patients: correlation of carotid artery intimamedia thickness with oxidative stress. J Diabetes Complications. 2008 Feb 22. Influence of vitamin E supplementation on endothelial complications in type 2 diabetes mellitus patients who underwent coronary artery bypass graft. J Diabetes Complications. 2008 Jan 3. Evaluation of the effect of oxidative stress and vitamin E supplementation on renal function in rats withstreptozotocin-induced Type 1 diabetes. J Diabetes Complications. 2008 Apr 22.Food selection based on total antioxidant capacity can modify antioxidant intake, systemic inflammation, and liver function without altering markers of oxidative stress. Am J Clin Nutr. 2008 May;87(5):1290-7. J Diabetes Complications. 2008 Apr 2. Supplementation of alpha-tocopherol improves cardiovascular risk factors via the insulin signalling pathway and reduction of mitochondrial reactive oxygen species in type II diabetic rats. Free Radic Res. 2008 Mar;42(3):261-71.Dual therapy with statins and antioxidants is superior to statins alone in decreasing the risk of cardiovascular disease in a subgroup of middle-aged individuals with both diabetes mellitus and the haptoglobin 2-2 genotype. Arterioscler Thromb Vasc Biol. 2008 Mar;28(3):e18-20. Plasma and dietary vitamin E in relation to insulin secretion and sensitivity. Diabetes Obes Metab. 2008 Mar;10(3):223-8.Gamma-tocopherol supplementation alone and in combination with alpha-tocopherol alters biomarkers of oxidative stress and inflammation in subjects with metabolic syndrome. Free Radic Biol Med. 2008 Mar 15;44(6):1203-8. Effects of vitamin C supplementation on antioxidants and lipid peroxidation markers in elderly subjects with type 2 diabetes. Arch Gerontol Geriatr. 2007 Dec 10.

- Another unique antioxidant that has been studied extensively in diabetes is **alpha lipoic acid, (also called thioctic acid**,) a B-vitamin-like substance made in the body from the essential fatty acid linoleic acid. It also has a role in energy production, as it is required in two places in the TCA cycle. It is very benign, and the level that is generally agreed as being **most likely to bring about positive effects in diabetes research has been 600 mg/day.** A randomized, double-blind, placebo-controlled, multi-center trial showed that alpha lipoic acid at an oral dosage of 800 mg/day for 4 months significantly improved cardiac autonomic neuropathy in type 2 diabetic patients. (Treat Endocrinol. 2004;3(1):41-52.)

This is one of the three supplement substances that were described earlier as being more expensive, and it is usually available over the counter in 50 mg pills. A prescription for a higher dose pill would facilitate things. One area in which alpha lipoic acid has been most effective (and most studied) is in peripheral neuropathy research, but it now looks very promising in several areas of diabetes complication research. For example, the following are examples of the reports on alpha lipoic acid and diabetes published just from late 2007 through July 2008:

[Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. Diabetologia. 2008 Jul 29. Early lipoic acid intake protects retina of diabetic mice. Free Radic Res. 2008 Jul;42(7):613-7.An endogenous dithiol with antioxidant properties: Alpha-lipoic acid, potential uses in cardiovascular diseases.] Ann Cardiol Angeiol (Paris). 2008 Jun;57(3):161-5. Pharmacological significance of alpha lipoic acid in up to date treatment of diabetic neuropathy] Med Arh. 2008;62(1):45-8Lipoic acid: a novel therapeutic approach for multiple sclerosis and other chronic inflammatory diseases of the CNS. Endocr Metab Immune Disord Drug Targets. 2008 Jun;8(2):132-42. Ability of alpha-lipoic acid to reverse the diabetic cystopathy in a rat model. Acta Pharmacol Sin. 2008 Jun;29(6):713-9.Mitochondrial nutrients improve immune dysfunction in the type 2 diabetic Goto-Kakizaki rats. J Cell Mol Med. 2008 Apr 9.Painful diabetic neuropathy: treatment and future aspects. Diabetes Metab Res Rev. 2008 May-Jun;24 Suppl 1:S52-7.Switching from pathogenetic treatment with alpha-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients. J Diabetes Complications. 2008 Apr 8.Treatment of diabetic neuropathy and neuropathic pain: how far have we come? Diabetes Care. 2008 Feb;31 Suppl 2:S255-61.Protective effects of R-alpha-lipoic acid and acetyl-L-carnitine in MIN6 and isolated rat islet cells chronically exposed to oleic acid. J Cell Biochem. 2008 Jul 1;104(4):1232-43.Management of painful diabetic neuropathy: what is new or in the pipeline for 2007? Curr Diab Rep. 2007 Dec;7(6):409-15.Curative effect of alpha-lipoic acid on peripheral neuropathy in type 2 diabetes: a clinical study] Zhonghua Yi Xue Za Zhi. 2007 Oct 16;87(38):2706-9. Lipoic acid ameliorates oxidative stress and renal injury in alloxan diabetic rabbits. Biochimie. 2008 Mar;90(3):450-9. R-alpha-Lipoic acid and acetyl-L: -carnitine complementarily promote mitochondrial biogenesis in murine 3T3-L1 adipocytes. Diabetologia. 2008 Jan;51(1):165-74. Effect of vitamin C and lipoic acid on streptozotocin-induced diabetes gene expression: mRNA and protein expressions of Cu-Zn SOD and catalase. Mol Cell Biochem. 2008 Feb;309(1-2):109-16.Effects of alpha-lipoic acid on endothelial function in aged diabetic and high-fat fed rats. Br J Pharmacol. 2008 Mar;153(5):894-906Impaired apparent ion demand in experimental diabetic retinopathy: correction by lipoicAcid. Invest Ophthalmol Vis Sci. 2007 Oct;48(10): 4753-8.Diabetic neuropathy: new strategies for treatment. Diabetes Obes Metab. 2008 Feb;10(2):99-108.Efficacy of alpha-lipoic acid against diabetic cataract in rat. Jpn J Ophthalmol. 2007 Jan-Feb;51(1):10-3. Diabetic painful neuropathy: current and future treatment options. Drugs. 2007;67(4):569-85. Review.The effect of alpha-lipoic acid on symptoms and skin blood flow in diabetic neuropathy. Diabet Med. 2007 Sep;24(9):1034-8. Alpha-lipoic acid may improve symptomatic diabetic polyneuropathy. Neurologist. 2007 May;13(3):164-7.]

- Another potent antioxidant with other roles in energy metabolism is **Ubiquinone – Coenzyme Q-10.** It is very safe and helpful in a number of applications, but it is also more expensive and a prescription might be helpful for this reason. CoQ10 treatment significantly improved deranged carbohydrate and lipid metabolism of experimental chemically induced diabetes in rats. The mechanism of its beneficial effect appears to be its antioxidant property.

[Antioxidant level and redox status of coenzyme Q in the plasma and blood cells of children with diabetes mellitus type 1. Pediatr Diabetes. 2008 Dec;9(6):540-5. Hemodynamic effects of fenofibrate and coenzyme Q10 in type 2 diabetic subjects with left ventricular diastolic dysfunction. Diabetes Care. 2008 Aug;31(8):1502-9. Coenzyme Q(10) and alpha-lipoic acid supplementation in diabetic rats: conduction velocity distributions. Methods Find Exp Clin Pharmacol. 2008 Jun;30(5):367-74 Coenzyme Q(10) and alpha-lipoic acid supplementation in diabetic rats: conduction velocity distributions.Methods Find Exp Clin Pharmacol. 2008

Jun;30(5):367-74 Oxidative burden in prediabetic and diabetic individuals: evidence from plasma coenzyme Q(10).Diabet Med. 2006 Dec;23(12):1344-9. Biol Trace Elem Res. 2006 Jan;109(1):25-34. Diabetes Res Clin Pract. 2006 Apr;72(1):100-3. Acta Diabetol. 2005 Dec;42(4):179-81. Curr Neurovasc Res. 2005 Dec;2(5):447-59.

Research into the control of free radical production or "quenching" them after they are formed, has shown antioxidants to have promising roles in kidney health, eye circulation, lens and retinal health, circulation of blood to the extremities, wound healing, peripheral neuropathy, erectile dysfunction, the development of gestational diabetes, and birth defects. It's time to seriously consider adding antioxidant protection to our standard protocols. (Am J Obstet Gynecol. 2006 Feb;194(2):580-5. J Soc Gynecol Investig. 2005 Dec;12(8):549-57. Free Radic Res. 2005 Dec;39(12):1285-93. Med Hypotheses. 2006;66(1):38-44. Br J Biomed Sci. 2005;62(2):71-6.)

Part Three: Reducing the severity of inflammation that has been shown to be associated with diabetes

Inflammation is now being recognized as a significant contributor to heart disease and to tissue damage in general. **Poor control of diabetes especially results in an increase in inflammation.** Besides being a special problem in diabetes, this has been found to be true for many conditions that have an autoimmune component, such as rheumatoid arthritis, MS and inflammatory bowel disease. In addition to inappropriate messages sent to tissues to increase inflammation (e.g. as a result of an autoimmune condition), inflammation results from any chronic disturbances in normal fuel metabolism, such as that seen with diabetes or excessive alcohol consumption.

Altering the ratio of omega-6 to omega-3 polyunsaturated fats appears to be an important step in achieving health for most Americans, and especially so in diabetes. [n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005 Mar;105(3):428-40.]

Americans tend to eat about 10 g of omega-6 fat for every gram of omega-3 fat (that is, a 10-to-1 ratio.) The "Mediterranean diet" provides about a 4:1 ratio, and most healthy people would likely benefit from change in this direction. For people with diabetes, MS, and other hyperinflammatory conditions, it has been suggested that a ratio of 2:1 may provide additional benefit.

It is now recognized that many people the ability to efficiently convert vegetable essential fats (18 carbon linoleic and linolenic acids) to critical fats used to make a variety of important substances.) These are the 20 carbon fats EPA and ARA (used to make prostaglandins, thromboxanes, leukotrienes and prostacyclins) and the 22 carbon DHA (a primary fat of a healthy brain.) **This means that some folks are much more dependent on their diet to assure adequacy of these key substances.** This observation is behind recommendations that **"ready-to-go" sources of these fats, like fish or fish oil supplements** have important health benefits for minimizing complications of diabetes, risk of cancer and heart disease, and in promoting a healthy outcome of diabetic pregnancy.

This defect in producing the 20-22 carbon length fats from the shorter fat forms derived from plants, may be a significant contributor to the inappropriate hyperinflammation. For more information, references and specific recommendations, please see "Aunt Cathy's

Guide to Nutrition: Omega-3 Fats and Other Lipids." **(Omega-3 and Omega-6 Fats references are too many to put in the text, so they follow at the end of this paper.)**

Part Four: Helping to stabilize excessive fluctuations of blood sugar

Some individuals sometimes have a problem with fluctuating glucose levels in spite of following the diet, exercise and medication program very carefully (e.g. what some people used to refer to as **"brittle"** diabetes.) In the past these people were suspected of "cheating" on the diet, since we could not explain the phenomenon. Unfortunately, this accusatory response is still common in some settings.

Increasing knowledge of the effects of other **differences in types of carbohydrates consumed and factors affecting absorption** have led to some changes in our globally accepted recommendations. For example, sucrose is not looking quite so automatically bad, and the carbohydrate in the form of high fructose corn syrup is looking worse. The movement toward **whole grains/whole foods** has improved both the **nutrient:CHO ratio**, resulting in an improved magnesium and chromium intake, as described above. Increasing the intake of **soluble and insoluble fiber** in foods has positive effects, although we are quick to assume that it is the **fiber** in a "high fiber diet" that does all the good, when the diet clearly alters many other nutrition parameters as well. In any case, we no longer perceive orange juice and an intact orange to be nutritionally identical in regard to the diet for diabetes, and we now regularly use a system of **carbohydrate counting** in place of the more rigid (and much less effective) "exchange system" for meal planning.

Improved understanding of the fate of specific carbohydrate-containing foods as described above is lending some light to this puzzle, resulting in exploration of concepts such as **genetic differences** in people's metabolism, and the "**glycemic index**" of foods and meals.

One other important piece of the puzzle is less well known among health professionals, so I will address it here in some detail. It has been found that **relative inadequacy of carnitine exists in some people with diabetes.**

Additionally, there is increasing evidence that supplemental carnitine can be of significant help in prevention or improvement of a number of complications of diabetes. For example, in a recent study, [Determination of free L-carnitine levels in type II diabetic women with and without complications. Eur J Clin Nutr. 2007 Jul;61(7):892-5] the average serum-free L-carnitine levels in diabetic patients with complications was almost 25% lower than in diabetic patients with no complications. On the basis of the study results, the researchers suggested that "carnitine supplementation in diabetic patients, especially in patients with diabetes complications, might be useful."

[The heterogeneity of diabetic neuropathy. Front Biosci. 2008 May 1;13:4809-16. Evaluation of the efficacy of propionyl-L-carnitine versus pulsed muscular compressions in diabetic and non-diabetic patients affected by obliterating arteriopathy Leriche stage II. Int Angiol. 2008 Jun;27(3):253-9. Effects of L-carnitine on obesity, diabetes, and as an ergogenic aid. Asia Pac J Clin Nutr. 2008;17 Suppl 1:306-8. Preventive effect of acetyl-L-carnitine on the thermal hypoalgesia in streptozotocin-induced diabetic mice. Eur J Pharmacol. 2008 Jul 7;588(2-3):213-6. ATP production and TCA activity are stimulated by propionyl-L-carnitine in the diabetic rat heart. Drugs R D. 2008;9(2):83-91. Protective effects of R-alpha-lipoic acid and acetyl-L-carnitine in MIN6 and isolated rat islet cells

chronically exposed to oleic acid. Acetyl-L-carnitine in diabetic polyneuropathy: experimental and clinical data. CNS Drugs. 2007;21 Suppl 1:13-23; discussion 45-6. J Cell Biochem. 2008 Jul 1;104(4):1232-43. Diabetes-induced bradycardia is an intrinsic metabolic defect reversed by carnitine. Metabolic agents in the management of diabetic coronary patients: a new era. Int J Cardiol. 2008 Jun 23;127(1):133-4. Metabolism. 2007 Aug;56(8):1118-23. L-Carnitine inhibits protein glycation in vitro and in vivo: evidence for a role in diabetic management. Acta Diabetol. 2007 Jun;44(2):83-90. Effects of L-carnitine on RBC membrane composition and function in hyperinsulinemic rats. Ital J Biochem. 2007 Mar;56(1):53-60. Determination of free L-carnitine levels in type II diabetic women with and without complications. Eur J Clin Nutr. 2007 Jul;61(7):892-5. Carnitine deficiency in children and adolescents with type 1 diabetes. J Diabetes Complications. 2004 Sep-Oct;18(5):271-4 . Assessment of free L- carnitine levels in type II diabetic women with and without complications. Asia Pac J Clin Nutr. 2004;13(Suppl):S155.]

This has also been found to be a factor in a number of other health conditions, with special importance in kidney disease and high triglycerides … both of which are risk factors related to diabetes.

Normally, one makes an adequate amount of carnitine in the liver and kidney from methionine and lysine, and additional carnitine may be obtained from meat. (That's why it is called carnitine – it comes from "carne" which means meat in Latin and Spanish. Memory device: think of "chili-con-carnitine.") Individual differences in requirements, diet, genetic carnitine production, and the use of certain medications (like valproic acid for seizure control) can result in a relative inadequacy.

Carnitine is a key component of a cellular transporter called "carnitine palmitoyl transferase" which allows fatty acids to cross the mitochondrial membrane to be used as fuel to make ATP. Because inadequate carnitine impairs one's ability to move fatty acids into the mitochondrial membrane, symptoms can include lethargy, poor exercise endurance, poor muscle tone, cardiopathy, elevated triglyceride levels, and if applicable, breakthrough seizures. **The key feature that affects blood sugar** is the fact that there are times when we normally switch to burning primarily fat as a fuel source in order to spare glucose for the brain – sort of like having "dual heat" in your home: gas and wood. But if fat is unable to be burned because of carnitine inadequacy, a person will have to burn glucose that he/she really can't afford to burn. This results in an extremely low blood sugar, which then can trigger release of glycogen from the liver causing blood sugar to rebound up high. And if no glycogen is available to correct it, the low blood sugar can be injurious, and even life-threatening.

Bottom line: if a person has this kind of yo-yo blood sugar with no identifiable cause, a trial on carnitine would be a good idea. Getting a blood level is not necessarily helpful, because if it is low, then you will give some carnitine. If it is normal, blood levels do not necessarily reflect adequacy in the tissues, so if there are suggestive symptoms, one would want to do a trial anyway. The usual dose is 50-100 mg/kg/day divided into 3 doses (just because of the high osmolality,) maximum usually 3000 mg/day.

To do a trial in the presence of symptoms, there is no reason not to start at the 100 mg/kg level, as the working presumption of the trial is that tissues may be depleted. Starting too low and stopping too soon may mask a true effect. When I do a trial, we monitor selected symptoms for change, and usually the trial would be continued for at least a month even in the absence of symptom relief, in order to be sure that any deficiency would have been corrected to the point of detection of symptom change.

Carnitine is the other supplemental substance that requires a prescription for a trial and which can be expensive. Over-the-counter products are available, but their actual carnitine content is not assured, so at least for the trial, I would use the guaranteed product. It is also useful to consider the cost of carnitine supplementation against the cost of damage from blood sugar vacillation, and the impairment of energy production and endurance, etc., if the problem is not identified and corrected.

Part Five: Minimizing risk of developing other threats to health and well-being, including some conditions that are known to be exacerbated by diabetes.

There are a number of conditions for which people with diabetes are at increased risk. These include elevated homocysteine levels, depression, cardiovascular disease (including stroke), leg cramps, and general neuropathy. Some are related to medications, such as the effect of metformin (Glucophage) on vitamin B12 level. Other common problems that can cause trouble for people with diabetes (or anyone) are these: Proton pump inhibitors for GERD may also contribute to poor absorption of vitamin B12 from food, and seriously obese people with diabetes may have had (or plan to have) gastric bypass surgery, which can also compromise vitamin B12 absorption and absorption of many nutrients. These situations will need a closer look than usual among people with diabetes.

High triglycerides are known to be a risk factor for stroke in people with diabetes especially. Three of the nutrition factors described above are associated with correcting high triglycerides: inadequate chromium intake, a high ratio of omega-6 to omega-3 fatty acids, and a relative carnitine inadequacy are all potential contributors.

The omega-6 : omega-3 ratio is also getting a lot of attention in research into cancer, MS, heart disease and arthritis, and the recommendations are all in the same direction. For more information, references and specific recommendations, please see “Aunt Cathy’s Guide to Nutrition: Omega-3 Fats and other Lipids.”

Inadequate vitamin B6 and magnesium appear to be involved in diabetic neuropathy, and also in heart disease and leg cramps. Vitamin B6, folic acid and B12 are critical for preventing elevated homocysteine, a major contributor to stroke, and possibly to alzheimers. Folic acid inadequacy is associated with cancer of the breast, prostate and colon. It is also a contributor to depression and inadequacy also makes therapeutic interventions like SSRAs work much less well. Chronic antibiotic use and alcohol abuse both impair folic acid absorption. Certain groups of people have a genetic problem that requires special attention to folic acid. For example, among some people of Irish heritage, the MTHFR gene has been discovered that contributes to higher rates of certain birth defects, depression and alcoholism. (Please see “Aunt Cathy’s Guide to Nutrition: Folic Acid” and “Aunt Cathy’s Guide to Nutrition: Vitamin B12” for details, references and recommendations.)

Some studies with vitamin B6 have used levels of 50 to 100 mg to achieve a desired effect in people with diabetic neuropathy. This is much higher than the RDA of about 2 mg, but not near a level that might be a problem. This is especially true if one is hypothesizing

that their vitamin B6 requirements are in fact higher than in other people. Niacin (vitamin B3), riboflavin (vitamin B2) and thiamine (vitamin B1) and biotin are all being studied. B vitamins are generally among the least toxic vitamins – B6 is the only one documented to cause problems with high amounts, and that was only in the most sensitive people, and never at levels below 200 mg/day. Most people who experienced any tingling in the forearms (the symptom in question) were taking over 500 mg chronically. Some people find it safe, cheaper and convenient to take a "B-**100** Complex" tablet along with their general multivitamin with minerals, instead of trying to tinker with a lot of individual B vitamins. As always, check with your physician about applying any of these ideas to your own health circumstances.

As it has recently been found that serious chronic conditions like **celiac disease and hemochromatosis are much more prevalent in the general population** than has been previously thought, health professionals would do well to keep these two conditions in mind among people with diabetes. **There are some links between hemochromatosis and diabetes, between hemochromatosis and celiac disease, and between diabetes and celiac disease**. For example, according to a recent report, "higher iron stores (reflected by an elevated ferritin concentration and a lower ratio of transferrin receptors to ferritin) are associated with an increased risk of type 2 diabetes in healthy women independent of known diabetes risk factors." The **development of pernicious anemia is also a threat in people with Type I diabetes**, and it may fail to be recognized because the neurologic symptoms of B-12 deficiency are mistakenly attributed to diabetes complications. Please see my vitamin B12 handout for more specifics about this issue.

[Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA 2/2004; Coeliac disease and hereditary haemochromatosis: association and implications. Eur J Gastroenterol Hepatol. 2/2004; Hereditary haemochromatosis. QJM. 6/2004; Oxidative Stress, Beta Cell Apoptosis and Decreased Insulin Secretory Capacity in Mouse Models of Hemochromatosis. Endocrinology. 2004; Precipitation of iron overload and hereditary hemochromatosis after successful treatment of celiac disease. Am J Gastroenterol. 1/2000; Emerging concepts in celiac disease.Curr Opin Pediatr. 8/2004; Prevalence of celiac disease markers in a French cohort of children and adolescents with type 1 diabete mellitus. Ann Endocrinol (Paris). 4/2004; Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. Diabetes Care. 6/2004; Celiac disease associated with type 1 diabetes mellitus. Endocrinol Metab Clin North Am. 2004 Mar; others.]

Celiac disease, an autoimmune disease that is triggered by exposure to gluten in wheat, rye and barley is genetically more common among people with Type I diabetes. At our clinic, we screen children with Type I diabetes for hidden celiac disease with a blood test. (We also check children with Down syndrome, as they have an increased risk of both celiac disease and Type I diabetes. They have also been found to produce more free radicals than other people, and to sometimes benefit from carnitine supplementation.) In addition to the gastrointestinal problems that are the most commonly recognized symptoms of celiac disease (which can certainly affect absorption of many nutrients), it is now recognized that there are other less well recognized neurologic and dermatologic manifestations of celiac disease, and they could be complicating the recognition and treatment of neurologic and skin disorders thought to be primarily related to diabetes. Celiac is also by nature inflammatory and it also contributes to increased production of free radicals.

Both hemochromatosis and celiac disease are decidedly <u>not</u> rare as had been thought and both are very detrimental, so health professionals caring for people with diabetes should be alert for these problems. Hemochromatosis causes an increased risk of damage to organs

like the liver, pancreas and heart, and it also is known to contribute significantly to inflammation and production of free radicals. The dietary protocol in support of regular phlebotomy can be very helpful, as I have found that many health professionals are not familiar with the many nutrition adjustments that can be of great benefit. If interested in this, please see "Aunt Cathy's Guide to Nutrition: Hemochromatosis."

6) Minimizing the risk of <u>developing</u> diabetes

As discussed earlier, assuring adequacy of magnesium, chromium and vitamin K intake may make a big difference in whether or not Type II or gestational diabetes develops in an individual. In addition, there is a major nutrition problem that is looking extremely important to correct in order to decrease the development of diabetes of any kind.

<u>Type I Diabetes</u>:

There is a growing body of good evidence that **<u>inadequacy of vitamin D</u> in early life may be one of the triggers that brings on Type I diabetes among genetically susceptible children.** For example, in a study in Finland, children who had experienced vitamin D – deficiency rickets as infants were four times more likely to develop Type I diabetes. The data is accumulating all around the globe, and it is consistent with the well known observation that **the northern tier of the US (and places of similar latitude around the world) is known as the "Rickets Belt", the "MS Belt" and the "Type I Diabetes Belt."**

Latitude is the most obvious factor in vitamin D inadequacy, but many other people are at risk because of skin color, clothing that covers a person up, diet, and several other important factors. **For many reasons, vitamin D inadequacy is a very large public health problem that has not yet captured the attention of most health professionals. [I hope to be able to edit this last statement out in the near future.]** For more information, extensive references, and specific recommendations. please see "Aunt Cathy's Guide to Nutrition: My Current Top Five Easy Ways to Improve Your Family's Nutrition;" Aunt Cathy's Guide to Nutrition: Vitamin D – It's not just for bones any more;" and "Aunt Cathy's Guide to Nutrition: Nutrition Issues in MS."

<u>Gestational Diabetes</u>:

Gestational diabetes appears to develop less often among women with <u>more vitamin D and vitamin C</u> in their blood. A recent study showed a positive correlation of 25(OH) vitamin D concentrations with insulin sensitivity; they suggested that "vitamin D deficiency could be a confirmative sign of insulin resistance." In another study maternal 25OHD concentrations were found to be inversely related to fasting glucose in another study. [Maternal vitamin D deficiency, ethnicity and gestational diabetes. Diabetic Medicine. 25(6):678-84, 2008 Jun. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes/Metabolism Research Reviews. 24(1):27-32, 2008 Jan-Feb. Maternal plasma ascorbic Aaid (vitamin C) and risk of gestational diabetes mellitus. Epidemiology. 9/2004.]

Researchers theorize that other antioxidants may have a similar effect including other antioxidants, possibly. Other nutrients that appear to be involved as well are magnesium and chromium (as discussed earlier.) A side note: with so many young women being

overweight now, and because some will actually have unrecognized Type II diabetes, it will be important to begin checking for diabetes much earlier in pregnancy (preferably before conception) in order to minimize birth defects.

Women identified in a clinic as having gestational diabetes (which develops later in pregnancy) may actually have Type II diabetes all along. Additionally, people who are significantly overweight appear to need higher intakes to maintain a normal blood level of vitamin D. Please see "Aunt Cathy's Guide to Nutrition: Top 10 Issues in Nutrition for Pregnancy" for much more on this issue.

Type II Diabetes:

In the on-going women's health study (Harvard), the likelihood of developing Type II diabetes among 85,000 women over a 14 year period was about 25% **less** among women who ate about 1 oz of nuts or peanuts (rich **magnesium** sources) 4 times a week or more compared with those who ate them rarely. The same result was seen when the risk of diabetes was evaluated relative to highest and lowest magnesium intake itself from all sources.

Other studies suggest that inadequacy of **vitamin D** may contribute to Type II Diabetes as well as Type I, with additional roles in a wide variety of health problems. These include death from all causes, heart failure, cardiac arrest, cancer of the colon, prostate, pancreas and breast, MS, muscle/nerve pain that is often missed and diagnosed as fibromyalgia, rheumatoid and osteo arthritis, muscle weakness and falling (sarcopenia), fractures, osteoporosis, poor prenatal outcome, and much more. Assuring adequacy is easy, cheap and crucial to good health, and it is now recognized that vitamin D inadequacy is very widespread in the US and around the world. As diabetes increases risk of cardiovascular disease, it would be prudent to take the extra step to ASSURE that one's vitamin D level is adequate by getting an annual check of vitamin D stores during the winter. [I have much more information about vitamin D on MeritCare's website: www.meritcare.com key word: cathy breedon.] 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med. 2008 Jun 9;168(11):1174-80. Vitamin D in Health and Disease. Clin J Am Soc Nephrol. 2008 Jun 4..]

And, as discussed earlier, one's intake of **fruits and vegetables**, intake of **vitamin K**, and one's serum **vitamin C** level also appear to be factors in the likelihood of developing Type II diabetes.

7. Discovering the emerging miscellaneous effects of a variety of phytochemicals on the diabetic state.

Around the world and in the US quite a number of plants and their various "phyto-chemicals" ("plant chemicals") are being investigated for their ability to influence health in diabetes and in general. This is outside of the scope of this paper, as in general the properties being looked at are more of a pharmaceutical nature than a nutrition nature. But if you would like to get a taste of the kinds of studies being undertaken, simply log

on to Public Medline (www.nlm.nih.gov) and pick the box at the right that says "for health professionals." Then check the "Medline" box. You will see a box at the top of the screen in which you should enter search terms such as: diabetes plant or diabetes herb or diabetes phytochemical. You will find reports like this: "Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28,812 postmenopausal women" in the journal Arch Intern Med. 2006 Jun 26;166(12): 1311-6. The conclusion of this study was that "Coffee intake, especially decaffeinated coffee, was inversely associated with risk of type 2 diabetes mellitus in this cohort of postmenopausal women." That is, the coffee-drinkers had LOWER risk.

Here is just a sampling of the kinds of information available from the past few years. It's a big topic and there has been even more research in 2007-8 that I haven't had a chance to enter into this paper. If you are interested, just go to www.pubmed.gov and type the words "diabetes" and "phytochemical" in the search box.

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