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It seems that as the months go by, the bad news outweighs the good. The latest concerns the diagnostic bible used by most mental health care professionals as well as some physicians in general practice. As discussed in this issue, we are being told by reputable critics that the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-V, fifth edition) will cause a hyperinflation in overdiagnosis and overtreatment, and that it may soon come to pass that everyone in the developed world will be diagnosed with a mental disorder during their lifetime. But this is just one of the problems faced by those who desire to raise healthy children and remain in good health to a ripe old age. Even a partial list is long. We have little idea of what we are really eating, and the guardians of our safety in this area are dominated by commercial interests. The classical fox guarding the hen house. We are faced with fake "organic" foods, concealed GMOs in foods, supplements that do not contain what the label indicates, food labels designed to deceive, dangers from pharmaceuticals that are suppressed, drugs that in some cases have ridiculously exaggerated benefits, distorted accounts of clinical studies presented without proper perspective by the media, and hostility from those we entrust with our healthcare when alternative medicine is suggested. We are immersed in a sea of chemicals humans have never encountered before. Some are highly toxic, mimic hormones, are carcinogenic, and accumulate, but are rarely considered relevant during the diagnosis of health problems (see "What's Gotten Into Us?", McKay Jenkins, Random House, 2011).

Professional ability seems to follow the bell curve and for the healthcare system, it is user beware. As discussed in the book reviews in the last issue, some hospitals are so bad that most of the professionals who work there would never use the facility if sick, and some are so superb that the knowledgeable will even travel long distances for their services. And there is everything in between. Alternative and integrative medicine appears to offer significant benefits to those with the classical chronic diseases (see "Ultra-Prevention", Mark Hyman and Mark Liponis, Scribner, 2003), but the merits are drowned out by the chant "Quack, Quack, Quack" from mainstream medicine, seriously flawed studies or in some cases unrealistic or ridiculous demands for gold-standard evidence.

For generations there has been considerable trust in experts and expert opinion. There was no one else to rely upon. However, faith in health care is now being eroded by questionable oversight, inconsistencies, contradictions, drug companies convicted of criminal fraud, evidence of bias and conflicts of interest and even absurdities. Expert egotism, self-interest and thinking only in the box have significantly retarded progress. Turning to the internet is clearly risky business when attempting to address some of these problems. Many individuals are helpless, obviously unable to judge complex medical and scientific issues that are important and frequently with no one trustworthy to turn to.

This is the milieu in which DSM-V will function.

Also included in this issue is an excellent review of vitamin K and the benefits of supplementation by Maurice Mckeown, BDS, PhD, IHN's New Zealand correspondent.

And finally, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

MENTAL DISORDERS FOR EVERYONE

The Diagnostic and Statistical Manual of Mental Disorders (DSM) Fifth Edition (DSM-V) is at the printers. Published by the American Psychiatric Association (APA), it is a major source of income. The DSM is intended to be used by a wide range of health and mental health professionals including psychiatrists and other physicians, psychologists, social workers, nurses, occupational and rehabilitation therapists and counsellors. The DSM-III listed 256 disorders, up from 180 in the previous addition. DSM-IV has 365 and DSM-V is rumoured to have more.

In the December 4, 2012 issue of *Psychiatric Times*, Dr. Allen Frances, MD, head of the writing project for DSM-IV and Professor Emeritus of Psychiatry, Duke University, advises readers to ignore what he regards as the 10 worst changes in the new edition. These involve new mental disorders and changes to the definitions for existing ones.

- Disruptive Mood Dysregulation Disorder, which will turn temper tantrums into a mental disorder.
- Normal grief will become a Major Depressive Disorder which will medicalize and trivialize expected and necessary emotional reactions to the loss of a loved one.
- Everyday forgetting characteristic of old age will now be misdiagnosed as Minor Neurocognitive Disorder.
- Expanded definition of Adult Attention Deficit Disorder will likely result in widespread misuse of stimulant drugs for performance enhancement.
- New psychiatric illness Binge Eating disorder, i.e. excessive eating 12 times in 3 months.
- Changes in the definition of Autism which may lower rates of the disorder and impact services available.
- The change in definitions that lumps first-time substance abusers with hard-core addicts.
- Behavioral Addiction (e.g. sex and internet addiction). Disorders which involves making common, popular activities a mental disorder.
- Changes in Generalized Anxiety Disorder (and worries of everyday life) which obscure the already fuzzy boundary separating normal from a disorder.
- Changes in how DSM-V deals with Post Traumatic Syndrome Disorder which have the potential to increase the already existing problem of misdiagnosis.

The principal concern is overdiagnosis and overtreatment. The claim of the publisher, the APA, that DSM-V is a conservative document that will have minimal impact on the rates of diagnoses and consequent inappropriate treatment is dismissed by Dr. Frances. Also, DSM-V was never tested in a real-world setting. He further points out that all the DSM-V changes, except for Autism, loosen diagnoses and threaten to turn diagnostic inflation into hyperinflation. Millions of individuals with normal grief, gluttony, distractibility, worries, reactions to stress, temper tantrums (of childhood), forgetfulness in old age, and behavioral addiction will soon be mislabelled as psychiatrically sick and may be given inappropriate treatment. People with everyday problems will now have disorders that will further burden an already

overstressed system. They will also carry a label of mental illness.

Dr. Frances concludes his opinion piece with the statement, “DSM-V violates the most sacred (and most frequently ignored) tenet in medicine—First Do No Harm! That’s why this is such a sad moment.” He points outs that DSM is a guide, not a bible. His goal is to minimize the harm that may otherwise be done by unnecessary obedience to what he regards as unwise and arbitrary DSM-V decisions.

In a second article in *Psychiatric Times* (February 13, online), Dr Frances adds to the list what he describes as one of the biggest potential problems associated with DSM-V. The category at issue is called Somatic Symptom Disorder (SSD), and arises when a patient is medically ill and having difficulty coping or adjusting to the illness or the prognosis. A person will meet the criteria for SSD by reporting just one medical illness symptom that is distressing and/or disruptive of daily life and having just one of the following three reactions that persist for at least six months; (1) disproportionate thoughts about the seriousness of their symptom(s); (2) a high level of anxiety about their health; or (3) devoting excessive time and energy to symptoms or health concerns. Field trials done by APA found one in six coronary disease or cancer patients met the criteria for being mentally ill with SSD. Furthermore, one in four of those with irritable bowel syndrome or chronic widespread pain qualified as having SSD. In the public review of the DSM-V, SSD attracted more responses than almost any other category. The potential exists for a huge increase in prevalence of mental health diagnoses and all the problems generated including overmedication with highly dangerous drugs, labelling as mentally ill, reimbursement and employment and insurance problems. To quote Dr. Frances: “In short, the DSM-V as its now stands will add to the suffering of those already burdened with all the cares of having a medical illness.”

Some critics of the DSM writing process allege conflicts of interest involving ties of some of the writers with the makers of psychiatric pharmaceuticals. Dr. Frances points out that he knows the writers of DSM-V and defends them. In his opinion the document represents their sincere beliefs untarnished by financial conflicts of interest. However, he qualifies this by saying “Theirs is an intellectual, not financial conflict of interest that results from the natural tendency of highly specialized experts to overvalue their pet ideas, to want to expand their own areas of research interest, and to be oblivious to the distortions that occur in translating DSM-V to real life clinical practice (particularly in primary care where 80% of psychiatric drugs are prescribed).”

There is another big problem. In what appears to be the most significant and serious criticism of modern psychiatry, Dr. Peter Breggin, a renowned psychiatrist who has been an active and high profile critic of modern psychiatry for a number of years, has over a decade presented startling research and a contrary view of mental disease, summarized in a recent medical monograph *Brain-Disabling Treatments in Psychiatry* and a new book *Psychiatric Drug Withdrawal*. Breggin has been called “the conscience of psychiatry” for his efforts to reform the mental health field. In the cited monograph, he describes the brain-disabling and spellbinding effects of psychiatric drugs and then thoroughly documents his views with thirteen chapters of elaboration covering the entire field of mental disease. Breggin takes exception to the view that the common mental diseases have a causal basis in biological imbalances, and he presents a diametrically different view, holding that the imbalances have never been proven and the action of psychopharmaceutical intervention involves altering and damaging the brain, sometimes permanently and in fact creating imbalances. The changes which occur create the impression of benefit through alterations in symptoms and behavior, but benefit is an illusion. This view resonates strongly with the observations of parents and spouses as they watch a family member progressively decline on psychiatric polypharmacy until the individual is no longer the same person and no longer lives in the real world. Breggin’s contrary view, which is evidence based, has staggering ramifications, especially as DSM-V threatens to significantly expand overtreatment. This brings us back to Frances’ point—First Do No Harm.

CURES FOR DIABETES. A STATUS REPORT

TYPE 1 AND TYPE 2 DIABETES

Type 1 diabetes (T1D) results when an autoimmune reaction destroys sufficient pancreatic beta cells such that insufficient insulin is available to control glucose metabolism and this hormone must be supplied via injection. The triggers for the autoimmune reaction remain somewhat obscure. Eventually virtually all the insulin required must be exogenous and many T1Ds encounter difficulties in glucose control with episodes of hypoglycaemia which can be dangerous. As even Banting, the co-discoverer of insulin pointed out, using insulin to control T1D is not a cure for the disease by most definitions of the word.

Obesity and type 2 diabetes (T2D) are closely interrelated in that risk factors such as poor diet and physical inactivity lead to weight gain and cause insulin resistance in important insulin sensitive tissues, particularly skeletal muscle, liver and adipose tissue. Insulin resistance increases the insulin levels required for cellular glucose metabolism, since insulin mediates glucose crossing of the cell wall. Insulin resistant diabetic patients generally have a positive energy balance, high fat and carbohydrate intake, increased abdominal adipose tissue, elevated free fatty acids and increased secretory products of fat cells mediating inflammation. Insulin resistance is common in obese patients but diabetes is not always present because of augmented insulin production which offsets the impaired insulin action. T2D develops when progressive pancreatic beta-cell dysfunction occurs and there is eventually a failure to secrete adequate amounts of compensatory insulin. Eventually the individual crosses the threshold of fasting blood glucose or the long-time average blood glucose (HbA1c) that qualifies for the diagnosis of diabetes.

About 90% of diabetics are type 2 and constitute a huge public health problem due to the serious nature of the associated complications which burden healthcare systems and destroy the quality of life. These include increased risk of cardiovascular disease, kidney disease leading to the need for dialysis, damage to the retina which can lead to blindness, and circulation problems leading to highly impaired peripheral circulation, failure of even minor injuries to heal, gangrene, and the risk of amputations. While the risk of complications is directly related to the circulating glucose levels, attempts to reduce the risk of most complications by intensive blood glucose control, including mortality, have been mostly unsuccessful.

CURE DEFINITIONS[1]

A cure for T1D must return the patient to normal. Adequately functioning beta cells must be present and protected from autoimmune damage. Normal glucose metabolism must be present without the use of any medication, including insulin. Thus the fluctuations in blood glucose must correspond to that on individuals free of diabetes or prediabetes and meet, for example, ADA requirements for being diabetes free.

A cure for T2D must involve the restoration of normal glucose metabolism without need for diabetic medications or insulin. The patient must meet ADA definition of no diabetes, and experience blood glucose fluctuations during the day that are normal. Successful normalization of glucose levels through pharmaceutical intervention cannot be regarded as a cure since it addresses only the concentration of a marker and has no impact on most complications which represent the reason for treating T2D.

According to these criteria, cures have been achieved in all of the approaches listed below, except stem cells. The number of successes is limited. Durability is generally unknown. The impact on long-term diabetic complications is also unknown, but some complications of diabetes are seen to diminish after curative treatment. Prevalence of long-term side effects of the various protocols is unknown.

APPROACHES TO CURING DIABETES

PANCREATIC CELL (ISLET) TRANSPLANTS FOR T1D

The most recent version of this protocol was pioneered by the Clinical Islet Transplant Program, University of Alberta, under the direction of A.M. James Shapiro. In 2000 they

reported seven consecutive patients with T1D who were unable to control their disease with insulin and underwent islet transplantation, and all achieved insulin independence with daily fluctuations in blood glucose varying between about 60 and 140 mg/dL.[2] The protocol (called Edmonton) involved harvesting islets containing pancreatic beta cells from pancreases obtained from brain-dead donors. After purification and preparation, cells were injected via a catheter inserted in the portal vein. At autopsy, the islets are found in the liver. Immune suppression is necessary to prevent rejection. The transplant protocol has a significant rate of adverse side effects.[3] As of 2011, over 750 islet transplants had been performed in over 30 international centers.[4]

In an update, Shapiro mentions that while early transplants were not particularly durable, now centers doing this protocol are achieving insulin independence for > 5years after transplant.[4] However, the supply of eligible donors is small, and the current protocol requires more than one donor. Shapiro suggests that if single-donor transplantation can be achieved, the technique will become more accepted and will have a major impact overall as an effective treatment option for T1D. Islet transplants are also attractive after kidney transplants in diabetics since immune suppression is already required. This highlights the trade-off associated with any transplant, having to live with the potential adverse effect of immunosuppressants.

PANCREAS OR PANCREAS-KIDNEY TRANSPLANTS FOR T1D

Pancreas transplantation can provide normalization of blood glucose control but there is the risk associated with the surgical procedure and the requirement of antirejection drugs to sustain pancreas function. Advances in surgical outcomes and immunosuppression have also made pancreas transplantation a more attractive option for those with T2D.[5] There are three options; simultaneous pancreas-kidney transplant, pancreas after kidney transplant, or pancreas alone.

In a summary of experience over a decade with pancreas transplants (156) in patients with severe diabetes with or without kidney transplant at Wake Forest Baptist Medical Center was recently published.[6] Excellent medium term outcomes were achieved with >90% of patients alive, >90% of surviving patients dialysis free, >80% of surviving patients insulin free, and nearly 90% of surviving patients exhibiting satisfactory beta-cell function. Pancreas transplant has also been found to improve or stabilize retinopathy and have a beneficial impact on neuropathy, but studies are very limited. Stabilization or regression of diabetes related kidney disease in patients transplanted only with a pancreas has been observed although the evaluation of benefit is complicated by the toxicity of immunosuppressive agent cyclosporine.

STEM CELLS

The use of stem cells appears to still have a long way to go before it becomes an accepted and adopted approach. Ideally the stem cells will be such that they will not be rejected. Thus recipients must be the source of cells which are eventually converted in to beta cells. Autoimmune reaction needs to be controlled or the new beta cells will suffer the same fate as the original ones. There is a potential for helping both T1D and T2D.[7]

METABOLIC SURGERY (BARIATRIC)

Surgical modifications of the digestive system have been used to treat obesity and morbid obesity with dramatic weight loss, and this can be accompanied by a decrease in progression to diabetes or a return to normal glucose metabolism as indicated by blood sugar levels and variations throughout the day. The beneficial impact on blood sugar levels in diabetics can occur rapidly after surgery but before weight loss has occurred.[8]

The most commonly performed bariatric surgery is the Roux-en-Y gastric bypass. It results in the resolution of T2D in approximately 80% of obese patients, where resolution is defined as clinical normalization of glucose parameters (fasting blood glucose and HbA1c) and discontinuation of all diabetic medications including insulin. This remission can be long term and would qualify as a cure. However, the mechanisms by which these surgeries provide T2D resolution are not clear and there are clearly both weight dependent and independent mechanisms at play.

Metabolic surgery involving by-pass or redirected flow profoundly alters many aspects of the digestive process and the hormonal

signalling that occurs throughout the stomach, duodenum and small intestine. Mal-absorption occurs which requires supplementation to avoid serious vitamin and mineral deficiencies which can result in distinct pathologies.

In contrast with banding, metabolic surgery is irreversible and has generally been restricted to a last resort for the treatment of the obese and those with morbid obesity who are unable to significantly reduce weight with diet and lifestyle. Many are diabetic and if not are at high risk of becoming diabetic.

These drastic procedures can also result, in a limited number of cases, in late onset hypoglycemia serious enough to require surgical reduction of the size of the pancreas. Bariatric surgery has mostly been studied in obese or very obese individuals. Very limited studies exist for individuals with BMI < 30. It is also offered to only a small percentage of those who might benefit. It can both prevent progression to diabetes, or return diabetic or prediabetic patients to normal glucose metabolism with no medications, and thus offers a potential cure.

SUGAR. A HEALTHY NATURAL FOOD OR A TOXIC SUBSTANCE?

In the U.S. per capita sugar consumption as of 2011 was estimated to be 78 pounds per person per year, mostly from cane and beet sugar (sucrose) and high-fructose corn syrup (glucose plus fructose). This figure is considerably lower than the 2000 number of 90 pounds, partly because of a revised estimate of waste, which is controversial (USDA figures). The 78 pounds converts to about 35 kg or about 400 cal/day, but this is an average and thus there are many individuals consuming considerably more. For comparison, typical diets are about 2000 calories but with a considerable range. Thus some may get more than 25% of daily calories from sugar. Before the advent of agriculture, humans obtained sugar mainly from fruit and honey, one controlled by seasonal availability, the other guarded by unfriendly bees.

Sucrose consists of molecules glucose and fructose joined together, 50% glucose, 50% fructose. It is broken up during metabolism in the duodenum to yield the individual sugar molecules which rapidly pass into the circulation. Glucose is only partly metabolised in the liver and mostly metabolized throughout the body as the primary fuel source for cells via a process mediated by insulin. It is the so-called blood sugar which diabetics monitor. Fructose, also called fruit sugar, on the other hand is almost completely metabolized in the liver. Glucose metabolism in the liver is regulated by a feedback mechanism, but this is not true for fructose which can provide a rapid influx of energy substrate for the liver which must be metabolized. What happens is a bit complicated, but a common result is the production of triglyceride deposition in fatty tissue (causing obesity) and in muscle and liver tissue resulting in insulin resistance and dyslipidemia. In feeding studies, fructose consumption increases visceral fat which drives cytokine production and predisposes to the development of type 2 diabetes, the metabolic syndrome and cardiometabolic disorders. High levels of circulating glucose can induce insulin resistance and eventual pancreatic beta cell burn out causing type 2 diabetes with concomitant micro- and macro-vascular complications. Thus the major issues raised by high levels of sugar are obesity, diabetes and the metabolic syndrome with their associated comorbidities. There is also an issue with cancer.

A diet considered by some to be healthy would have both starches and sugars as sources of glucose with sucrose a minor source compared to non-sugar carbohydrates. Fructose would come from fruit and sucrose. Another source of glucose and fructose is high fructose corn syrup (HFCS) which is cheaper than sugar, and was introduced into food and beverages a number of years ago. HFCS also contains an approximately 50-50 mix of glucose and fructose, except that the sugars are free. In addition, diets high in carbohydrates, especially simple starches, increase post meal blood glucose. Foods containing sugar or HFCS add to the glucose load. The physiologic response to high circulating glucose is increased secretion of insulin, but for some, this ultimately results in insulin resistance requiring more and more insulin until an overstressed pancreas is

unable to deliver, beta cells fail, and the end result is type 2 diabetes. The insulin resistance is also aggravated by fat deposition triggered both by high carbohydrate and high fructose consumption.

Insulin resistance is clearly an important issue. It is now evident that insulin resistant patients, whether obese or lean, have fat accumulations in the liver. This brings us back to fructose. If a researcher wants to create insulin resistance in, for example, laboratory rats, all that is necessary is to feed them pure fructose or enough sucrose. Their livers convert the fructose into fat which accumulates and insulin resistance and the metabolic syndrome follow. Furthermore, it is reversible when sugar intake is limited.

In a recent review, Stanhope and Haval compare fructose and glucose with regard to issues introduced above.[9]

- In a feeding experiment a beverage providing 25% of energy requirements from either glucose or fructose was consumed for 10 weeks by older overweight/obese adults. Weight and fat gain was similar, but fructose consumption resulted in mainly visceral deposition (13% change from baseline) whereas glucose yielded mainly subcutaneous fat deposition (3% change from baseline). Visceral fat deposition is generally regarded as more closely associated cardiovascular disease and type 2 diabetes than subcutaneous deposition.
- Fasting insulin was unchanged in the glucose group but increased in the fructose group.
- Insulin sensitivity was significantly decreased in the fructose group but unchanged in the glucose group.

Both the changes in fasting insulin and glucose and the change in insulin sensitivity in the fructose group were undesirable in the context of cardiovascular disease and type 2 diabetes. On the basis of these observations and other results discussed in the review, they conclude that adverse effects associated with drinking commercially available sugar sweetened beverages are largely attributable to the fructose component. Since sweetening with glucose is not a practical option and artificial sweeteners, especially aspartame, appear to introduce their own serious side effects,[10] the only remaining option is simply to reduce sucrose or HFCS consumption. If consumption is at the U.S. national average, then the reduction needed is quite large. In 2009 the American Heart Association released dietary guidelines for added sugar which set a decreased limit at 100 cal/day for women and 150 cal/day for men.[11] The published statement makes mention of some of the points raised above but emphasizes the limitation as a calorie justification rather than the issues raised above. Some researchers in this field would reduce intake of all forms of sugar to near zero. One of the reasons is the connection with cancer.

Many readers have probably heard the phrase “cancer loves sugar.” Obesity, diabetes and the metabolic syndrome are risk factors for the incidence of cancer. First reported in 2004, the connection is not controversial. In a review just published, Orgel and Mittelman list 8 cancer types where incidence is associated with insulin resistance manifest by type 2 diabetes and 4 linked to the metabolic syndrome.[12] Implicated were esophageal, colorectal, pancreatic, liver, kidney, breast, endometrial, bladder and cervical cancers. Consistent with this is the common view that a large percentage of cancers are caused by the Western diet and lifestyle.

The mechanisms postulated are highly complex and not fully understood. What has emerged is that many human cancers come to be dependent on insulin to provide the glucose fuel and raw materials they need to grow and multiply. The role of insulin and insulin-like growth factor and related growth factors is to provide signals for the processes. Some cancer cells have mutations that enhance the cellular influence of insulin whereas others simply utilise the elevated insulin associated with obesity, the metabolic syndrome and type 2 diabetes. One view is that many precancerous cells would never acquire the mutations that render them malignant if it were not the driving force of insulin causing them to overload with blood sugar and metabolize.[12,13] In the opinion of Dr. Lewis Cantley of Harvard Medical School, up to 80% of all human cancers are driven by either mutations or environmental factors that enhance or mimic the effect of insulin on precancerous cells.[14]

As knowledge expands concerning growth factors and metabolic pathways implicated in cancer cell growth, there will no doubt be growing interest in developing targeted pharmaceutical therapies. However, a straightforward approach might simply involve dealing with elevated insulin levels and insulin resistance. Thus there are now studies appearing in the literature that examine the impact of ketogenic diets on cancer progression, in general and specifically in brain cancer.[15-17] These involve both human and animal studies and are providing encouraging results. This is actually the same problem facing the diabetic who is trying to initiate remission with diet, a subject discussed in recent issues of IHN. Sugar consumption is obviously a related issue. Gary Taubes in an article in the *New York Times Magazine*, reports that two prominent researchers studying the cancer—insulin connection have stopped eating sugar whenever possible. One said "sugar scares me."[14]

WHEN TO TAKE VITAMIN D SUPPLEMENTS

Humans evolved to obtain vitamin D mostly through solar UV-induced photosynthesis. However, in many populated regions on earth, solar generation of vitamin D is negligible from late fall to early summer and for those who live mostly inside, the same situation exists year-round. Thus vitamin D deficiency is common, is attributed to increased risk of numerous disorders and supplementation is now widely recommended although controversial. The blood marker is 25-hydroxyvitamin D (25(OH)D) and 30 ng/mL (75 nmol/L) is frequently cited as the threshold below which deficiency is recognized and ≥ 50 ng/mL (125 nmol/L) is considered desirable.

Not all deficient individuals respond to supplementation even at high doses (e.g. 5000-10,000 IU/day). In 2010 scientists at the Cleveland Clinic examined the hypothesis that this was partly due to the fat-soluble nature of vitamin D and that absorption would be depend on when relative to meals the supplement was taken.[18] To test this hypothesis they recruited subjects that were unable to significantly increase their 25(OH)D levels. They were taking the supplement either on an empty stomach or with a small meal, usually breakfast or lunch. They were advised to continue with the same dose (1000 to 50,000 IU/day of either D2 or D3) but take the vitamin with the largest meal of the day, generally dinner. At baseline, 25(OH)D levels ranged from 22-39 mg/mL. After the dietary protocol change, the range was 35-74 ng/mL Seventeen subjects were involved and no stratification according to D2 vs. D3 was made. D2 is generally less effective but may be given in larger doses. The design of the study did not allow examination of the relative importance of the macronutrient content of the diet and the increased vitamin absorption.

At the same time, a group at Tufts University were examining the impact of dietary fat type on response to vitamin D supplementation.[19] A year earlier it has already been suggested that long-chain polyunsaturated omega 3 fats not only did not enhance absorption but in fact appeared to decrease it.[20] The Tufts University group confirmed this and also found that diets rich in monounsaturated fatty acids improved the effectiveness of supplementation with vitamin D3. Saturated fats appeared to also have a negative impact, but the result was not statistically significant.

The question of high- vs. low-fat meal on 25(OH)D levels was examined by Raimundo *et al.*[18]
Thirty-two physicians were divided into two groups, one of which was given a high-fat meal, the other a low-fat meal during which they also received a 50,000 IU dose of vitamin D3. Levels of 25(OH)D were measured before the meal and at 7 and 14 days. This one high fat meal resulted in a significant increase in levels whereas the low-fat meal produced a null result. Between 7 and 14 days after supplementation the levels were still increasing in the high-fat group.

The issue being addressed is very important. No other nutrient, drug or hormone has the wide-reaching health benefits of this vitamin. Low vitamin D is a risk factor from almost all age-related diseases and plays a role in resistance to viral infections. For example, one

randomized, placebo controlled study involving supplementation of women with 1000 IU/day of vitamin D3 for 2-4 years yielded a greater than 50% reduction in the risk of a number of cancers with the number needed to treat of 21 to prevent one cancer.[21] It is thus unfortunate that better studies and more data are not available concerning the issue of absorption. In addition, the above studies suggest that vitamin D deficiency may be one of the adverse side effects of low-fat diets and the low-fat or near zero-fat way of life considered by some to be ideal. Nevertheless, the take-home message appears to be, supplement with vitamin D during the largest meal of the day or the meal containing the largest amount of monounsaturated fat. Foods high in monounsaturated fat include meat, avocados, olive oil, nuts and dark chocolate. The message for researchers is that vitamin D status is a confounder to be reckoned, a difficult challenge when dose dependence of 25(OH)D levels may depend on diet and dose timing.

The observation that diet and vitamin D absorption appear related also suggests that it is not a simple matter to optimize absorption given the limited guidance from studies. This would seem to increase the importance of measuring levels, especially in mid or late winter to ascertain the success of supplementation. However, not everyone can take high doses of vitamin D, including those with pre-existing kidney disorders and those prone to hypocalcaemia. Since a physician must order the 25(OH)D tests, these issues can be addressed.

Finally in the "you can't win" category, it was reported a long time ago that vitamin D increases absorption of iron, zinc and toxic metals including lead, cadmium, aluminum and cobalt. However, avoiding ingesting toxic metals should be a priority for everyone and even vitamin C increases the adsorption of iron. Lead, cadmium and aluminum also block the synthesis in the kidney of the 1,25-dihydroxyvitamin D, the metabolite of 25(OH)D most frequently linked with health benefits of optimum vitamin D status.[22] Incidentally, a recent study found that only 10% of calcium supplements manufactured by different multinational companies met US standards if taken in recommended doses. Levels were highest in chelated supplements.[23]

MATERNAL FOLIC ACID USE AND AUTISM IN CHILDREN

A study just reported online in JAMA and featured in the evening news involved over 85000 children over a mean follow-up period of 6.4 years (range 3.3—10.2).[24] The maternal exposure to folic acid started prior to pregnancy. The unadjusted relative risk (odds ratio) was 0.51 and the confounder adjusted relative risk was 0.61, or about a 40% relative reduction in the risk of childhood autism. Both were statistically significant. The 40% risk reduction makes good news copy. However, the absolute risk reduction was 0.11% (0.21%--0.10%) which yields a number of mothers needed to treat (NNT) of 910 to prevent one case of childhood autism over the study period. When the endpoint was severe language delay, the NNT was 2500 to prevent one case. While the absolute prevalence numbers were given in the abstract and tables, no mention of the huge NNT result was made in the abstract or discussion. How many readers of the JAMA article or the abstract bothered to calculate it? How many reacted by regarding the 40% as great evidence for folic acid supplementation? The call for the emphasis of NNT continues to fall on deaf ears and the featuring of relative risk reduction continues to seriously distort and confuse issues in medicine and deceive the public. While there are other important reasons for taking folic acid prior to conception and during pregnancy, the impact on autism appears close to insignificant.

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RESEARCH REPORT

Vitamin K - Future Promise

by Maurice Mckeown, BDS, PhD

Our New Zealand Correspondent

Many years ago I was doing my doctoral research in a department whose main focus was bone research. One of the issues most perplexing was the tendency of the body, as it aged, to become calcified in all the wrong places. We were also aware that in some parts of the body calcification did not occur when required. Today we have a much better insight into these problems.

The subject of this, less than comprehensive, review is of course vitamin K. There has been substantial and potentially beneficial research on this vitamin in recent years; yet it has not received star billing like vitamin D.

Medical science has produced some impressive (and expensive) procedures to combat cardiovascular disease and osteoporosis. There are even a few drugs from Big Pharma which seem to be of modest value in both treatment and prevention. Yet prevention is so much better than cure and nature is much smarter than Big Pharma scientists.

Vitamin K was discovered by Danish scientist Henrik Dam in 1929. Vitamin K was, and still is, known as the clotting drug - (K for coagulation in both Danish and German) in the minds of most GP's who combat unwanted clotting with vitamin K antagonists as anticoagulants in thrombosis victims. Vitamin K is also prescribed for newborns who may lack proper blood clotting function.

We are now just beginning to understand that vitamin K has many other beneficial roles in the body. Most of this research is focused on vitamin K2, a molecule quite similar to K1 but with a different tail structure. Perhaps it is best to ask a series of questions.

Where do we get K vitamins in our diet?

Vitamin K1 comes from green leafy vegetables and is thus abundant in healthy diets. It is also present in legumes and some vegetable oils. The primary sources of K1 in our diet appear to be spinach, kale, broccoli and brussel sprouts. Vitamin K in spinach may have some absorption limitations. Vitamin K1 is absorbed into the body in the small intestine with the help of bile salts.

Vitamin K2 is a much less common constituent in most diets. The K2 molecule has a long straight tail. The length is designated by the MK number. There doesn't seem to be a detailed understanding of the virtues of the different versions. Note that MK-4 can be made in the human body whereas MK-7 cannot. The quantity in meat and egg products is negligible. Meats contain the short chain menaquinones which appear to equate to vitamin K1 in biochemical relevance. Cheeses contain the longer chain varieties.

There are small amounts in meat, eggs, specific cheeses and other dairy products. The notable exception is the Japanese diet where the fermented soy bean product natto contains large quantities. If you eat it regularly that should suffice. Unfortunately natto is not popular on the Western palate. I have to report that I don't find it unpleasant- just uninteresting! One hundred grams of natto could contain around 1000 mcg of MK-7 plus some MK-6 and 8.

In contrast a serving of chicken might contain eight mcg, one of beef around one mcg and an egg might contain five mcg in its yolk. Hard (fermented) cheese contains small amounts of MK-4 and nearly 70 mcg of MK-8 and 9. Unfermented cheeses contain no K2. It should be noted that fermentation of any food, in itself, is not a guarantee of vitamin K content. The production of vitamin K is the result of the action of specific bacteria. An example of this is the Indonesian fermented soy food tempeh, which does not seem to contain any K2. Recently the use of K vitamins by different bacteria has been studied as a possible method of inhibiting their function.

What is the relationship between K1 and K2 in our bodies?

It has been known for a long time that K1 can be converted to K2 in the body. It has also been known that bacteria in our gut can manufacture K2. Studies in germ free rats have shown that their bodies can convert K1 to MK-4 (one form of K2), thus bacteria are not necessary for this step. Unfortunately this reassuring news has recently been tempered by new information which has demonstrated that the K1 to K2 conversion is limited in our bodies - even in conditions where K1 intake is high. Also there is good reason to suppose that although gut bacteria can and do produce K2, little of the K2 produced gets into the body proper because the bacteria retain much of it for their own uses and absorption into the body is not thought to be favourable to fat soluble elements in the lower gut. Animals that eat their own faeces do seem to have sufficient K2!

What are the main modes of action by K2 in the body?

The best known roles for K2 are in the prevention of arterial wall calcification and in bone integrity. In effect K2 acts as a cop directing traffic at a busy junction. It ensures that calcium ends up in bone and not in the walls of the arterial system. Science is still working on what goes on in bone. The bone protein osteocalcin (discovered in 1975) is activated by a process called gamma-carboxylation. That process is made possible by K2 and indeed K1. If no carboxylation occurs then calcium cannot bind to the protein to initiate the calcification process. Measures of the degree of carboxylation seem to be the best way of assessing the vitamin's status in the body.

It is likely that K2 has a specific binding protein in the nucleus of the osteoblast (a bone making cell). As an added advantage the tail of the K2 molecule, unlike that of the K1 molecule, suppresses the formation of osteoclasts which are bone removing cells. It is also very likely that K2 has other advantageous functions in bone. A known one is its inhibition of a prostaglandin involved in osteoclast formation. It is important to point out that these functions of K2 in bone appear to be independent of the carboxylation process which is involved in the vitamin's site-specific actions mentioned above.

The calcification of arterial tissue (hardening of the arteries) has been viewed as an irreversible process. Additionally the study by the Maastricht research group has demonstrated that arterial calcification is reversible, in rodents at least, with vitamin K. The relative merits of Vitamin K1 and 2 have not yet been fully explored. It seems from this Dutch study that massive doses of K1 may be required to reverse arterial calcification while K2 may provide similar benefits at physiological doses. (1)

What other functions might K2 have in the body?

K2 has been implicated in the optimum functioning of various body systems. This suggests that its deficiency may contribute to various disease states. For example, a recent study suggests it may be able to correct a mitochondrial genetic malfunction in fruit flies, which has been associated with

Parkinson's disease.(2) Interestingly Parkinson's patients have a higher risk of bone fractures and they can be treated with large doses of K2 to reduce fracture risk and enhance vitamin D status.(3)

K2 deficiency is also suspected to be involved in the formation of varicose veins. (4)

K2 has been shown to protect the liver from cancerous change in subjects with cirrhosis and it may help prevent advanced prostate cancer.

Administration of K2 (not K1) to lab rats has resulted in increased testosterone levels. (5)

K2 seems to have the ability to inhibit ectopic calcification. For example it has been shown that it can inhibit calcification in the dermis of the skin. (6)

Similar processes may be involved in its anti-arthritic benefits. (7)

K2 may have specific anti-cancer activity in the prostate. The EPIC study, that very large European study on diet and health, has found that longer chain menaquinones are associated with a reduced risk of advanced prostate cancer and shorter chain ones eg. from meat which are mildly protective for non-aggressive forms of the disease. (8)

Low vitamin K levels appear to result in impaired pancreatic function in rats. The pancreas is rich in K thus its deficiency may be a diabetic risk factor in man. (9)

What form of vitamin K is best?

Vitamin K1 has not been shown to have valuable cardio and bone protecting activity. The preferred form of K2 is the MK-7 variety. Supplementation of MK-4 has not resulted in enhanced plasma MK-4 levels, while supplementing with MK-7 on a regular basis results in substantial and prolonged increases in tissue levels and reductions in uncarboxylated osteocalcin. It has also been claimed that the best source of MK-4 in the body is MK-7! The actions of MK-4 appear to be largely confined to the liver. See http://www.vitaminK2.org (Maastricht Research group website)

How can we use K2 to provide health benefits?

It is reported that all K2 supplementing studies have demonstrated improvements in bone density while studies using K1 have not done so. The mainstream medical drugs, notably the bisphosphonates and hormone replacement therapies have by contrast shown very small benefits. Their limited success is probably due in part to their mode of action, which seems only to address one aspect of the problem - the resorption side of the equation in bone. It should also be pointed out that the question of bone integrity is not just an issue involving the amount of calcium in bone. The other elements in living bone are just as important. Thus improved bone mineral density, seen on bone scans as a result of standard treatments, does not necessarily mean the bone is stronger and more resistant to fracture.

There are two key proteins in bone - osteocalcin and osteopontin, both of which are products of osteoblasts (bone forming cells). They are joined together. When bone is subject to a blow the bond between them deforms. This seems to be a protective mechanism. More severe trauma leads to rupture of the bond. It seems that osteocalcin is the point of fracture, so bone deficient in osteocalcin is more prone to fracture. Osteocalcin can only be incorporated into bone in its carboxylated form, which in turn can only be produced when sufficient vitamin K is present. (10)

In the cardiovascular system K2 has been shown to minimize calcification in arteries. In one animal study it seems to have reversed pre-existing calcification. (See above)

At least two studies have raised concerns that supplementation with calcium and usually vitamin D

may increase the risk of cardiovascular disease in women taking the combination to try to prevent osteoporosis.(11) It has also been proposed that the addition of vitamin K2 might eliminate this risk. (Cees Vermeer - Letter to the *British Medical Journal* 1 Feb 2008)

Vitamin K may have other benefits beyond bone and the cardiovascular system. Mentioned above is possible protection against prostate cancer. It has also been shown to protect the liver from cancerous change in subjects with cirrhosis and it may help prevent advanced prostate cancer. Thus we must infer some form of general anti-neoplastic role. (12) (13)

Should everyone take K2?

Cees Vermeer has observed that in their K2 investigations they found no one who had optimum carboxylation levels. This suggests that we would all benefit from MK-7 supplementation. It does not of course answer the question of what might constitute an acceptable level of carboxylation. Vermeer suggests that daily intake of around 180 mcg may be necessary for an ideal degree of carboxylation to be achieved. (Interview with Dr Mercola - see video library on his website http://www.mercola.com)

In the Western diet both vitamin K1 and K2 are lacking. In the case of K1 (phyloquinone), we get most from a few leafy vegetables and spices. It seems highly unlikely that regular dietary sources can provide quantities which would lead to optimum carboxylation of osteocalcin in bone. A study in which young healthy adults were given large amounts of supplemental phyloquinone confirmed that quantities far in excess of dietary intake were required for carboxylation to approach 100%.(14)

There are of course many unanswered questions. How high a carboxylation level is required to protect bone integrity? What are the K1 absorption capabilities of older healthy people; not to mention those with compromised health? (It seems that absorption of K2 is not a problem) How are we to address the problem of those taking vitamin K antagonists for blood clotting problems?

Studies in western countries have all shown that food sources provide little K2. The only solution seems to be supplementation or perhaps we all could develop a taste for natto where available! Read vitamin K2 supplement labels carefully. They will say vitamin K2 - but there are different types. If the label only says Menaquinone it is almost certainly MK-4. If it says "from Natto" it is MK-7. The relative merits of the different menaquinones do not seem to have been fully explored. The numbers refer to the length of the tail of the molecules concerned. It is clear from the work of the Maastricht research group that MK-7 has a much longer half-life in the body than MK-4 due to differences in the way it is metabolized.

It is clear that K2 provides protection against arterial calcification and also enhances bone health. Dutch research suggests that women who have diets with higher levels of K2 (not K1) have less arterial calcification.(15) It has also been shown that the higher menaquinones may provide substantial protection from cardiovascular disease in older women. Natto and fermented cheeses and some other dairy products, provide longer chain menaquinones. (16)

The prevalence of osteoporosis and indeed cardiovascular disease suggests that many older people should take a K2 supplement. Japanese research has demonstrated that high levels of K2 are required in the plasma of older women (above 70 years) to achieve adequate levels of carboxylation implying that carboxylation efficiency is age-related. (17)

Those who have been taking antibiotics, which indiscriminately kill their intestinal bacteria, are known to have dramatically lower levels of vitamin K2 in their gut. The possible effect on bodily K2 levels is unclear. (18)

Very large doses of vitamin k have been used to treat osteoporosis in Japan for many years and do not appear to have resulted in serious side effects. Mega doses of vitamin K have not resulted in increased clotting risk.

The bones of the young

Vitamin K intake in children is low probably because foods like broccoli, spinach and kale are not popular. Unfortunately their vitamin K needs are higher than adults because osteocalcin levels in growing bone are 8-10 times greater than adult levels. It has been shown that improving vitamin K status results in stronger denser bone in children. (19) Could we speculate that denser bone in youth might alleviate bone loss in old age?

Ageing issues

We know that the body's ability to convert K1 to K2 falls dramatically as we age. We also know that it is likely that increasing age causes an increased requirement for K2 in order to maintain an appropriate level of carboxylation of osteocalcin. (20) Elderly women have been shown to have less carboxylated osteocalcin, but the reasons are unclear and may not be related to vitamin K deficiency. (21)

It would seem prudent to add a K2 supplement, in the form of MK-7, to our diets. Fifty to one hundred mcg daily seems appropriate as a starting point. This may be particularly relevant for those suffering cardiovascular or osteoporosis problems. The mainstream approach to bone loss and restoration is to prescribe calcium supplements (with the possible addition of vitamin D and magnesium), or to use hormone replacement therapy. The value of these strategies seems limited. Controversy exists about whether extra calcium supplementation is a safe procedure. It has been suggested by the Maastricht research group that any adverse effects on the cardiovascular system might be mitigated by concurrent supplementation with MK-7 as mentioned above.

I would like to briefly address the issue of vitamin k antagonists designed to inhibit blood clotting. Warfarin-based products have proved very valuable in controlling unwanted clotting. Yet it has to be admitted that they do have a tendency to encourage arterial calcification in the long term. Some newer substitutes may be better in some respects, but can have disastrous consequences as their effects cannot be immediately reversed. This can result in hemorrhaging patients requiring massive blood transfusions. Vitamin K researchers are well aware of these issues. The Maastricht group has done a study where they have measured coagulation components in the blood of normal subjects taking varying amounts of vitamin K2. They have concluded that daily consumption of no more than 45 mcg of K2 is unlikely to affect coagulation markers and may indeed provide greater stability to vitamin K intake and thus warfarin dosage. Does this mean that warfarin users can take small doses of K2 while continuing with their medication; thus protecting their arteries and valves? Alas we do not know and your doctor may not want to find out. There may be alternative anti-coagulation systems in the pipeline. The rutinosides could be one of them. (22)

In conclusion

We are far from a full understanding of the role of K vitamins in our bodies. There is good reason to suppose that they play an important, perhaps vital role, in maintaining optimum health. They appear to have very low toxicity. It seems to me that we cannot await future studies to further elaborate their benefits. I suggest we should ensure that we have enough vitamin K2 by supplementing with MK-7.

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