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During routine physical checkups or examinations it would be extraordinary if the physician did not check off blood tests for glucose metabolism and blood lipid status. Not to check fasting blood glucose, HbA1c and the blood lipid panel (total cholesterol, LDL and HDL cholesterol and triglycerides) would be tantamount to malpractice in the view of mainstream medicine. But patients should also expect that three other markers would also be checked. Vitamin D and B12 status are clearly important. In this issue a good reason for the latter is discussed. Also, as the discussion of iron overload in this issue suggests, it might be a good idea to have the ferritin blood level measured. If it is elevated, or even high compared to the US average, then blood donation becomes attractive. If problems are uncovered by measuring these three markers, they can be addressed with much greater expectation of benefit than, for example, a somewhat elevated LDL level in someone free of heart disease. Some would argue that thyroid function via at least TSH should also be routinely measured.

How about a PSA test? There is no simple answer. In fact this represents a classical dilemma caused by an intrinsically imperfect test. An informed decision requires a discussion with the doctor. False positives suggesting prostate cancer can cause a lot of grief.

The main theme of this issue is iron overload. Iron status does not appear to have a very big profile in modern medicine. Unless symptoms suggest the presence of hemochromatosis, the potential dangers associated with even mildly elevated iron levels appear to be generally ignored. The focus is on anemia. The discussion in this issue examines iron overload and its association with cardiovascular disease and diabetes, but in fact the list of diseases impacted by elevated iron levels is long and encompasses the major chronic diseases of aging. Iron can be a very bad actor, mainly due to oxidative damage, and furthermore, humans do not have a mechanism for maintaining optimum levels via excretion of excess iron. Numerous foods and drink from red wine to shrimp and red meat, dark chocolate yogurt, and dark green leafy vegetables contain significant amounts of iron. Very large amounts of iron are found in fortified cereals. Thus it is possible to have an iron overload simply due to excessive intake, especially heme iron from meat consumption

Other topics discussed in this issue include diabetic drugs and pancreatitis, dangers of GM corn and soy, the use of folate to treat depression, and a drug-drug interaction involving statins and antibiotics.

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 a healthy and happy summer,

William R. Ware, PhD, Editor

Highlights

IRON OVERLOAD, CARDIOVASCULAR DISEASE AND DIABETES

INTRODUCTION

It is well established that humans need a certain level of iron for health, but higher levels are potentially toxic.[1] Iron is the central element of the heme molecule and is an essential constituent of hemoglobin and necessary for oxygen transport. Thus there are complex regulatory mechanisms present to control the body stores and maintain an approximate balance between dietary iron absorption and daily losses. However, there is no homeostatic mechanism for excreting excess iron to maintain a certain level. Public perception is mostly focused on anemia, a justified concern, and not on overload, as can be seen by the internet emphasis on helping one find good sources of iron. Iron deficient anemia is common in premenopausal women due to food choices and inadequate intake of bioavailable iron. On the other hand, iron overload can be attributed to excessive intake, especially heme iron.

Elevated iron stores over time which can release active iron which has been implicated in the pathogenesis of cancer, neurodegenerative disorders, diabetes, infections and atherosclerosis. Of particular interest is the observation that women have a very low incidence of heart disease prior to menopause but once this milestone has been passed, the risk increases to approach that of men. While this has been attributed to hormonal effects rather than iron, there is a much lower level of iron stores in premenopausal women compared to post-menopausal women, and this has been demonstrated to be an independent risk factor for cardiovascular disease.

Iron is mostly sequestered as ferritin, an ubiquitous intracellular protein that both stores iron in a non-toxic form, and releases it in a controlled manner. The blood level of ferritin is the most commonly used marker for the magnitude of iron stores. The mean levels found in American men in the population study NHANES III were about 150 ng/mL, for menstruating women ages 17-49, 25-35 ng/mL, and for post-menopausal women ages 50-59, 60 ng/mL and for ages > 60, about 90-100 ng/mL. These numbers illustrate the huge gender difference and raise concerns that the normal modern male level or the level found in older postmenopausal women may pose some danger of toxicity. A typical reference range for normal is 22—322 ng/ mL. Data will be presented below suggesting that the upper limit appears well above optimum.

Dietary iron is either heme related with the sources being meat, or inorganic. Heme iron is much more efficiently absorbed (15-35%) than inorganic (2-20%), and in addition, the nature of the food or drink can influence the absorption. For example, absorption of the iron in red wine or iron in a meal accompanied with red wine is inhibited by the polyphenols in the wine and only a few percent is absorbed. In attempting to limit iron intake, meat, especially organ meats are the most important to minimize.

For inorganic iron, fortified cereals are at the top of the list followed by various beans and then spinach. Perspective can be gained by knowing that typically the excretion of iron is about 1 mg/day and looking at iron content tables in the Internet while taking into account absorption. Vitamin C strongly increases iron absorption. Chelators (see below) taken with a meal decrease the absorption. Medical concerns typically focus on anemia, but when intake and subsequent absorption exceed excretion, iron stores can gradually build to levels that can significantly impact health.

TOXICITY OF IRON

The toxicity of iron is related to its role in producing oxidative damage. Iron catalyzes the production of the highly toxic and reactive hydroxyl radical as well as other reactive oxygen species (ROS). When these overwhelm the antioxidant capacity, damage occurs which has been related to diseases of aging such as atherosclerosis, cancer, diseases of autoimmunity, Alzheimer's disease, Parkinson's disease, diabetes, and in general diseases of inflammation.[2] Statistically significant correlations have been observed between high ferritin levels and elevated inflammatory marker (cytokine) levels.[3] One view is that the dangers of excess iron operate through inadequately liganded (tied up) iron ions. When the ions are liganded they are unreactive but weak ligand formation leaves some reactive free iron.

IRON AND CARDIOVASCULAR AND PERIPHERAL VASCULAR DISEASE

Given that the association between elevated iron stores and cardiovascular and peripheral vascular disease is somewhat controversial, it is important to examine the effects on such endpoints as mortality, heart attack and stroke when an attempt is made to lower these stores. Studies to date employ blood removal (phlebotomy) or blood donation. The results are summarized in the table below. For the Meyers 1998 study, data was collected for 3 years. In the Salonen 1998 study, donors, some of whom had prevalent CHD, were identified if they had donated ≥ one time in the 24 months prior to baseline. In the Meyers 2002 study, frequent healthy donors with no active heart disease who had donated more than one unit per year for two years prior to follow-up were compared with casual donors who had donated only a single unit over a three year prior to follow-up. In the other donation studies, the comparison was with donor vs. non-donor. Zacharski and colleagues studied patients with severe peripheral vascular disease many of whom had cardiovascular disease and a third had diabetes. The researchers attempted to keep the intervention group at ferritin levels between 25 and 60 ng/mL by removing blood periodically) whereas the control in the age range held at about 110 ng/mL. This last study was a randomized intervention trial. The results are summarized in the following table.

STUDY	GENDER	AGE	EVENT	RRR	NNT	YEARS	METHOD
MEYERS[4] 1997	M 66%	40-85	CV	50%	13	6	DONATION RECALL
SALONON[5] 1998	M 100%	42-60	AMI	88%	9	9	DONATION RECALL
MEYERS[6] 2002	M & F	52-64	CV	38%	19	10	DONATION FREQUENCY
ZACHARSKI[7] 2011	M 100%	43-61	MORTALITY COMPOSITE	52% 22%	11 17	5.5	PHLEBOTOMY ≤78 VS. ≥78 ng/mL

(CV), Cardiovascular event, (AMI), acute heart attack, NNT number needed to treat to prevent one event. Composite-- death, heart attack or stroke.

Subgroup analysis of the study upon which the Zacharski analysis is based has recently revealed that the benefits are in fact restricted to smokers. But this study involved secondary prevention.[8]

The relative risk reductions are mostly very large and supported by large absolute risk reductions which are reflected in the small numbers needed to treat over the duration of the study to prevent one event or the numbers engaging in the intervention needed to prevent one event. Another interesting aspect of the above table is that there were large effect sizes even in the studies where the donation rate was not well defined. Thus there appears to be strong evidence that lowering iron status as measured by ferritin or donor frequency produces remarkable and clinically important risk reductions. In the Zacharski study, the levels achieved in the intervention put the male subjects at the high end of the iron status zone characteristic of premenopausal women.

IRON STORES AND ATHEROSCLEROSIS

There appears to be only one study, recently published, where the association between ferritin levels and coronary atherosclerosis was the issue.[9] A group of 12,033 men underwent cardiac computed tomography in order to obtain their coronary calcium score (CACS). Only early atherosclerosis was examined using the threshold of CACS > 0. Increased ferritin concentrations were associated with the presence of coronary calcification, independent of traditional cardiovascular risk factors including the Framingham risk score, pre-existing vascular disease, diabetes, metabolic syndrome and low-grade inflammation. When quartile 1 was compared with quartile 4 for ferritin levels, the odds of having CACS > 0 was increased by 69% with a high level of statistical significance. This result was adjusted for confounding by using a model containing all conventional risk factors.

ASSOCIATION BETWEEN IRON LEVELS, DIABETES AND THE METABOLIC SYNDROME

The potential role of iron in the pathogenesis of diabetes is suggested by several observations.[10] (1) Increased incidence of diabetes is seen in patients with diverse causes of iron overload. (2) The reduction in iron load by either chelation or phlebotomy can improve glycemic control or reverse diabetes. (3) Dietary intake of heme iron (e.g. red meat) and concomitant increases in iron stores is associated with the risk of developing diabetes. (4) Insulin sensitivity and insulin secretion are increased by frequent blood donation. The molecular mechanisms are numerous and incompletely understood but include oxidative stress, modulation of adipokines and intracellular singling transduction pathways.[11,12]

It has been argued that the modest elevations of ferritin observed in diabetes may be a consequence of the disorder rather than a causal factor impacting insulin resistance and β-cell function and apoptosis.[13] However, evidence suggests otherwise. Excessive amounts of non-transferrin-bound iron, the form most susceptible to redox activity, are found in diabetic patients with a strong gradient for disease severity.[14] Furthermore, as will be discussed below, phlebotomy in type 2 diabetes results in improvements in glycemic control and insulin sensitivity which also supports the hypothesis that iron plays a pathogenic role.

Two recently published systematic reviews with meta-analyses have examined the association of diabetes incidence with ferritin levels. One study[15] reports a meta-analysis of 12 prospective or cross-sectional studies which analyzed ferritin levels and involved 4366 type 2 diabetes patients and over 41,000 controls plus 4 studies that measured heme-iron intake involving 9246 type 2 diabetics and about 180,000 controls. It was found that for the highest vs. the lowest category of ferritin level, the risk of diabetes was increased 66% in prospective studies and 130% in cross-sectional studies. A similar comparison for heme-iron intake yielded a 31% risk increase.

A second study[16] examined the association between the risk of diabetes and dietary iron intake in prospective studies. A meta-analysis of five studies gave a pooled relative risk increase of 33% in a comparison of the lowest vs. the highest heme-iron intake. For elevated ferritin levels, they found a 63-70% increase in relative risk in multivariable-adjusted models. There was no significant association with dietary intake and risk for non-heme or supplemental iron intake, a result consistent with the high bioavailability only of heme iron.

Incidentally, another study found a correlation between ferritin levels and the risk of diabetic retinopathy.[17]

A recent review and meta-analysis relates to the above. At issue is the association between red meat intake and risk of developing type 2 diabetes. A 19% increase was found per 100 g/day of red meat and a 51% increase per 50 g/day of processed red meat.[18]

For postmenopausal women (56-62 years of age) who typically have ferritin levels between 70 and 90 ng/dL,[19] data taken from one of the above studies[16] for the risk of developing type 2 diabetes are given in the table below according to the highest vs. the lowest ferritin quartiles.

STUDY	HIGHEST Q (ng/mL)	LOWEST Q (ng/mL)	ODDS RATIO DEVELOPING DIABETES
Jiang	≥107	<21	2.68
Forouhi	≥72	<18	2.55

It would seem that for women in this age group, levels just somewhat above the NHANES average already carry significant risk.

The metabolic syndrome (MetS) is recognized as a risk factor for diabetes. Population studies find an association between ferritin levels and the risk of MetS in the US,[20] Korea,[21] and Germany.[22] Ferritin levels are associated with the MetS in postmenopausal but not premenopausal Korean women.[23] High levels of ferritin in a Chilean population correlated not only with a 3-fold increase in developing MetS but also with high levels of oxidative stress indicated by serum markers, and there was a 21 fold increase in the development of this syndrome when the highest vs. the lowest quartiles were compared.[24]

CLINICAL USE OF PHLEBOTOMY TO REDUCE BODY IRON STORES

Both blood donation and phlebotomy can dramatically reduce iron stores[7,25]. Repeated blood-letting very efficiently lowers ferritin levels even if the initial values are very high such as seen in hemochromatosis. Withdrawal of between 5 and 10 mL of blood generally reduces ferritin by 1 ng/ml. One unit of blood equals 450-500 mL. Furthermore, no induced anima has been reported. The following studies are of interest:

- In a randomized controlled trial with metabolic syndrome patients, reduction of mean ferritin levels from 183 to 105 ng/mL using phlebotomy resulted in significant reductions in blood glucose, HbA1c, and systolic blood pressure. Changes in blood pressure and the insulin resistance index (HOMA-IR) correlated with ferritin reduction.[25]
- In a study comparing lacto-ovo vegetarians and meat eaters, the former were found to have mean ferritin levels of 35 ng/mL compared to 72 ng/mL for meats eaters and to have higher insulin sensitivity. When body stores of iron were lowered by phlebotomy in the meat eating group there was a 40% increase in insulin mediated glucose disposal.[26]
- The effect of phlebotomy on insulin resistance in a group of patients with non-alcoholic fatty liver disease and strongly elevated ferritin levels found a significant reduction in the HOMA-IR from 4.81 to 3.12 when ferritin levels were reduced from 438 to 52 ng/mL.[27]
- In a study designed to examine the pathogenesis of diabetes associated with mutations of the hemochromatosis gene, 17 carriers comprising 8 diabetics and 9 with normal glucose tolerance (NGT) were subjected to phlebotomy and the impact on insulin sensitivity and secretion investigated. Baseline ferritin levels were 942 and 1148 in the NGT and diabetic subjects, respectively. Ferritin targets were ≤ 100 ng/mL or ≤ 50 ng/mL depending on negative or positive evidence for iron deposits in the liver. The target levels were maintained and at 24 months the endpoint parameters measured. In both the NGT and diabetic groups, insulin secretion and insulin sensitivity increased. In

the diabetic patients, fasting glucose declined from 137 to 105 mg/dL (7.6 to 5.8 mmol/L), the latter being close to normal.[28]

- Studies prior to those discussed above also found that reduction of iron stores consistently produces an improvement in insulin sensitivity and β-cell function.[29,30]
- Advanced glycation end products are thought to play a role in the complications of diabetes and the basic biochemistry involves reactive oxygen species including those attributed to iron activity.[31]

CHELATION, THE ALTERNATIVE TO PHLEBOTOMY OR BLOOD DONATION

Oral chelation has been the traditional mainstream approach to iron overload for patients having pathological levels, and several prescription drugs are available. However, iron overloads involved in most of the studies discussed above are nowhere near those encountered in pathological iron overload. Furthermore, while studies, both interventional and observational, suggest target ranges for both men and women, optimum levels are clearly debatable. Chronic low-dose oral chelation therapy may be an important tool for the prevention and treatment of diabetic complications. Furthermore, oral chelation can prevent increased iron stores when absorption exceeds excretion.

If one wishes to use non-pharmaceutical interventions other than blood-letting to lower ferritin levels there are a number of "natural" iron chelators. N-acetyl cysteine is in fact a standard therapy for treating pediatric pathological iron overload, even in infants. Green tea extract, curcumin, silymarin, alpha-lipoic acid (or R-lipoic acid) and quercetin all have documented success in iron chelation.[32] These chelators also act to eliminate other toxic metals although for mercury it may help to add selenium to N-acetyl cysteine and lipoic acid. Curcumin was recently found to be a very good iron chelator.[33] A recent randomized controlled trial demonstrated the effectiveness of curcumin in significantly improving markers of glucose metabolism in diabetics.[34] It should be noted that these chelators can reduce zinc levels and therefore supplementation is indicated.

The results of the Trial to Access Chelation Therapy (TACT), a randomized, placebo controlled intravenous EDTA chelation trial, recently reported. Included were the results that for diabetics, there was a 39% relative risk reduction and a number needed to treat of 8 (median follow-up 55 months) found for the composite primary endpoint of total mortality, recurrent MI, stroke, coronary revascularization or hospitalization for angina.[35] EDTA chelation generally results in large increases in urine iron as well as other metals immediately post infusion.[36]

The TACT result is particular interesting since intensive glycemic control with multiple drugs and even the addition of insulin fails to impact cardiovascular or total mortality or almost all other complications associated with diabetics.[37-40] The dramatically lowered fasting blood glucose or HbA1c produced by intensive drug therapy may be viewed as successful control and treatment, but engenders false optimism while the pathogenesis of complications relentlessly progresses to ultimately yield clinical manifestations.

IRON STORES REDUCTION AND DIABETIC COMPLICATIONS

Studies on humans designed to examine this issue are limited. A 9-month study on diabetics using deferiprone oral iron chelation reduced ferritin levels from 144 to 59 ng/mL and improved kidney function was indicated by a decreased mean albumin/creatinine ratio from 187 to 25 mg/L.[41] In addition, a study involving the progression of diabetic nephropathy used a polyphenol–enriched, low-iron carbohydrate-restricted diet over 4 years. There was no significant change in HbA1c, but there was an absolute decrease in the incidence of serum creatinine doubling of 18% and a decrease in mortality or end-stage kidney disease of 18% over four years (number needed to treat over 4 years for either was 6).[42] Iron chelation due to the polyphenols (from red wine, tea and polyphenol enhanced olive oil) was probably partly responsible for reduced ferritin from 325 to 53 ng/mL and may have been a major contributor to these results.

CONCLUSIONS

Studies are clearly needed to establish optimum iron stores in both men and women in the context of not only diabetes incidence, progression and complications, but also for all inflammation-related chronic diseases, in particular those associated with aging. The upper reference level for normal is close to the threshold for hemochromatosis, a disorder which requires intervention. Furthermore, large clinical studies are needed to examine the impact of lowering iron stores on the incidence of clinical manifestations of the complications of diabetes, not just markers of glucose metabolism. Can aggressive iron stores reduction, perhaps with severe carbohydrate restriction, cure type 2 diabetes, i.e. eliminate need for any medication? This question should have high priority. There are clearly health issues associated with iron but one of the potentially effective interventions, blood donation, is free with almost no side effects. Iron stores as measured by ferritin can be dramatically lowered in most individuals without inducing anemia. Once past a certain age, the elderly are generally not eligible for blood donation and if elevated iron stores suggest merit in ferritin reduction, they may have trouble obtaining phlebotomy if their levels fall in the reference range for normal.

NEWS BRIEFS

DIABETIC DRUGS AND ACUTE PANCREATITIS. IS THERE AN ASSOCIATION?

Animal studies have strongly suggested that the drugs in the glucagon like peptide-1 group receptor agonists such as sitagliptin (Januvia) and exendatide (Byetta) can cause acute pancreatitis. Agonists bind to cell receptors and trigger a response. While this disorder is serious by itself, it is also implicated in the pathogenesis of pancreatic cancer, being in fact the commonest factor.

Exendatide and sitagliptin are also known as incretin mimetics and are used in treating type 2 diabetics who are unable to control their blood sugar levels with oral medication. Incretin is a natural hormone made by the body. It triggers the release of insulin after eating and thus reduces post-meal glycemia. Other actions of incretin include preventing the synthesis of glucagon, the hormone that induces the liver to release stored glucose, and slowing the rate of stomach emptying after eating.

A recent case-control study has examined the association of these drugs and acute pancreatitis in type 2 diabetics.[43] Cases (requiring hospitalization) and controls were drawn from administrative claims data available from Blue Cross Blue Shield Association databases in several states. For “any exposure” which included recent exposure and extended two years back, there were 87 cases in the exposed group of 1182 subjects (7.76%), and 58 in the control group of 1211 individuals (4.75%). When adjusted for confounding, these numbers resulted in a doubling in risk of acute pancreatitis. These drugs are widely used even though they carry “black box” warnings regarding pancreatitis and there is obviously the potential for significant increased incidence in those who take these two widely prescribed drugs.

The authors discuss a number of studies that fail to support their results, although there were problems in some studies regarding corrections for confounding. Two studies cited supported the current study, and one found a 6 fold increase in pancreatitis associated with the two drugs in question. An analysis published in 2013 by the U.S. Institute for Safe Medication Practices found that on combining studies on five incretin mimetics, the rate of pancreatitis was increased 25 times compared to the incidence in diabetics on other drugs. Recent articles in the British Medical Journal not only suggest that the risk of this class of drug has been underplayed, but they document the building pressure being put on drug companies to hand over all the data pertaining to pancreatic harm.

Readers are referred to an article in the *New York Times* (May 30, 2013, Business Day section) by Andrew Pollack which provides some interesting history related to the above. It also notes that drugs in this class account for more than $9 billion annual sales and are used by hundreds of thousands of individuals with type 2 diabetes. Pollack points out that there are more than 100 lawsuits representing 575 plaintiffs in the US claiming injury from Byetta.

Another issue concerns the risk/benefit ratio. Drugs are used to control glycemia in order to prevent the complications of diabetes. As discussed in previous newsletters, the evidence of benefit appears weak or non-existent when the occurrence of complications or diabetes-associated acute events are endpoints.

TOXICITY ASSOCIATED WITH FEEDING PIGS GM SOY AND CORN

Animal studies offer one of the few possibilities for investigating the potential toxicity of genetically modified (GM) foods in humans. A recent study form Australia and the US examined adverse effects associated with raising pigs on a diet of GM soy and corn, also termed GMO feed.[44] Pigs on this diet had a higher rate of severe stomach inflammation than pigs fed a non-GMO diet. The authors comment that given the widespread use of GMO feed for livestock as well as humans, this is a cause for concern. They comment that humans have a similar gastrointestinal tract to pigs, and these two GMO crops are widely consumed by people, particularly in the US, and it would be prudent to determine if the results of this study are applicable to humans. Somewhat of an understatement.

METHYLFOLATE EFFECTIVE IN TREATING MAJOR DEPRESSION

The pharmaceutical approach to depression generally involves the use of selective serotonin reuptake inhibitors (SSRIs). However, as discussed in previous issues of IHN, there is a strong and significant placebo effect and for mild and moderate depression SSRIs appear no better than placebos. For severe or major depression, the possibility that the improvements seen are also a placebo effect has been suggested.[45] When SSRIs do not produce improvement, the patients are termed *SSRI-resistant*. Polypharmacy may then follow.

A Study has just reported where L-methylfolate, generally considered preferable to folic acid when folate supplementation is an issue, was used as an additive (adjunctive) treatment for SSRI-resistant patients.[46] Two multicenter trials were reported which investigated the effects of the combination of methylfolate and an SSRI. Both trials were randomized and placebo controlled. The trials compared an escalated dose of methylfolate (7.5 mg/d for 30 days followed by 15 mg/day for 30 days) vs. a constant dose of 15 mg/day for 60 days. SSRI dose was kept constant. In the first trial, no benefit was found for adding methylfolate, but in the second where the constant higher dose was used, significant efficacy was observed compared to just the SSRI and placebo in both the response rate and degree of change in depression symptom score and symptom severity. The authors calculate the number needed to treat for response was approximately 6 in favour of the adjunctive methylfolate 15 mg/day treatment. There was no impact on remission but the treatment periods were short.

It is noteworthy that in this study the SSRI was not stopped. The reason presumably is that there would then be withdrawal symptoms, perhaps severe, which would confuse the issue.

Once an individual has been on antidepressant medication, abrupt termination is not an acceptable option. In fact, Peter Breggin, one of the most vocal and high profile critics of psychiatric medication except in the most severe cases, has just written a book detailing the problems of withdrawal and the protocols for accomplishing it safely.[47] Most of the material in this book is accessible to the lay reader.

In an accompanying editorial, It was pointed out that the association of depressive symptoms and folate deficiency has been known for five decades.[48] The have been numerous studies, both adjunctive with drugs and with folic acid (or methylfolate) used alone. Many produced positive results. Unfortunately, many studies that also looked at adverse side effects used folic acid rather than methylfolate whereas today, integrative and alternative practitioners use methylfolate. Folic acid, a synthetic "convenience" surrogate for folate, is only partially metabolized with the result that there is circulating un-metabolized folic acid which has unknown effects.

VITAMIN B12 AND COGNITIVE DECLINE

The classic presentation of B12 deficiency exhibits potentially serious blood related disturbances as well as neurological and psychiatric problems. A recent study examined the association between B12 and folate status and the decline in scores on the Mini-Mental State Examination (MMSE) in the Framingham Heart Study population.[49] Declines in the MMSE score directly relate to cognitive decline. The researchers examined the decline in the MMSE score over 8 years with special reference to the two lowest quintiles of plasma B12. It was found that cohort members with B12 concentrations between 187 and 257 pmole/L, the second quintile, had an accelerated rate of cognitive decline similar to the first (lowest) quintile. It was also found that having B12 levels in the first or second quintile in conjunction with high plasma folate or supplemental folate use predicts an especially high cognitive decline. However, plasma folate or consuming folic acid was not associated with cognitive decline in participants with B12 levels of 258 or greater. The association between high folate and accelerate decline is not clear since the Framingham cohort data were collected before mandatory fortification. Thus the subjects had low folate intakes. In fact, plasma folate greater than 59 nmol/L was found in only one participant with B12 levels less than 258 pmol/L. Folate deficiency was highly prevalent and high folate intakes were not in fact very high. The authors suggest the persistence of low combined vitamin B status suggests a malabsorption phenomenon.

The authors conclude by highlighting the importance of identifying low B12 status and finding and treating the cause in order to avoid rapid cognitive decline. Mandated folic acid in the diet may eliminate anemia, and with it fatigue, the most obvious manifestation of B12 deficiency in the elderly, thus allowing the deficiency to go undetected (the so-called masking effect).

STATIN TOXICITY FROM CLARITHROMYCIN AND ERYTHROMYCIN

The study to be described even made the front page of your editor's local newspaper. The issue here is the inhibition of an enzyme involved in the metabolism of certain statins such as atorvastatin, simvastatin and lovastatin, all widely used worldwide.[50] It turns out that clarithromycin and erythromycin are inhibitors of this enzyme and thus co-administration results in elevated levels of statins which theoretically could increase the risk and incidence of important side effects. These antibiotics are also widely used. This study looked at rhabdomyolysis (an acute muscle disorder), acute kidney injury, elevated potassium levels and all-cause mortality. The comparison was with azithromycin which does not inhibit the enzyme involved in statin metabolism.

When the researchers looked at the outcomes defined by hospital-based diagnostic codes which provided the 30-day risk, the number need to treat to produce one adverse outcome (i.e. to harm) was 5870 for rhabdomyolysis, 499 for acute kidney injury and 399 for all-cause mortality. When hospital based laboratory data was used instead, the 30 day risk translated into number needed to harm was 79 for acute kidney injury and 135 for elevated potassium

levels. However, the use of laboratory data resulted in only 47 cases of kidney injury vs., 10 control cases and 18 vs. zero cases for elevated potassium levels. All the numbers needed to harm were provided in the paper.

Thus there appears to be a need for a much larger study to generate more cases, narrow confidence intervals on the relative risks and resolve the huge discrepancy between the two data sets. In fact, to obtain a relative risk when the control was zero cases required "adjusting" zero to 1. Nevertheless, the biological plausibility of the drug-drug interaction is obviously compelling and this study should raise concerns and consideration of not pairing these antibiotics and statins.

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