

INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 241

OCTOBER 2013

22nd YEAR



In the July-August IHN the relationship between body stores of iron and diabetes and cardiovascular disease was discussed. This month's feature addresses the issue of the reference ranges for normal iron body stores and why the upper limit of these ranges does not reflect current knowledge regarding the blood ferritin levels thresholds associated with risk or the baseline levels in studies that demonstrate benefit from large reductions. This is reminiscent of the story of vitamin D where historically little attention was paid to the question of optimum levels, studies using insignificant amounts were used to discredit its importance in the eyes of mainstream medicine, and deficiencies were and still are widespread with serious health consequences. The challenge is to obtain some insight into what might be the optimum level of ferritin, the most commonly used measure of iron stores, if the goal is to maximize health and avoid chronic diseases. There can be no doubt that the importance of iron in the human system, its control, and adverse effects of too much iron are vastly underappreciated. It does not appear that ferritin, the accepted marker for iron status, in contrast to cholesterol and blood sugar, is routinely measured and if it is, the reference range for normal returned on the lab report makes no sense. The reference range for normal should have an upper limit which indicates minimal risk and values at or below this limit should indicate no benefit from lowering the marker. In fact, this is not the case, which is in sharp contrast to many other markers including measures of anemia, fasting blood sugar, glycosylated hemoglobin (HbA1c) and HDL, triglycerides, and LDL if one believes in the cholesterol hypothesis. Evidence will be presented which suggests that the optimum levels for both men and women are quite low and just somewhat above the ferritin levels which represent undesirable iron depletion, and that these levels are vastly lower than either the population means or the upper values of the reference range for normal. As was discussed in the July-August IHN, drastically lowering ferritin does not in general produce anemia and is easily accomplished by blood donation, or if that is impossible, by phlebotomy (blood-letting), and slower but effective reductions are possible with natural iron chelators.

Strategies for preventing, slowing or reversing coronary plaque are discussed in this issue. This is important because of the strong association between the extent of coronary plaque as measured by the coronary calcium scores, and acute coronary events. It is noteworthy that one of the most important interventions involves lifestyle issues, and that in addition, replete vitamin D status and low serum ferritin may be very important.

The third major topic in this issue is a major position statement from mainstream medicine concerning cancer overdiagnosis and overtreatment, a problem that is rapidly assuming a high profile. Particularly noteworthy is the proposal that ductal carcinoma in situ (DCIS) of the breast no longer be called either carcinoma or cancer. Since treatment of DCIS constitutes a major activity in oncology, and critics point out that the inevitable very high cure rates distort breast cancer treatment success statistics, this proposal is bound to be highly controversial.

In addition, a number of developments of current interest are discussed in News Briefs.

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 | |
|----------------------------------|-------|
| Coronary plaque progression | p. 6 |
| Focus on cancer over-treatment | p. 7 |
| Methanol ingestion in California | p. 9 |
| Long-term aspirin use and cancer | p. 9 |
| Diovan studies scandal | p. 10 |
| Vitamin D and breast cancer | p. 10 |
| Floroquinolone and nerve damage | p. 11 |

RISK OF TOO MUCH IRON SERUM FERRITIN LEVELS VIEWED AS NORMAL MAY PRESENT SIGNIFICANT HEALTH ISSUES

INTRODUCTION

It is well known that both low and high iron levels raise a number of health issues. Anemia is universally recognized, its threshold well defined and its treatment generally successful. On the other hand, elevated iron levels can be dangerous due to the production of reactive oxygen species and reactive molecules that can damage cells and thus cause organ and vascular damage. However, there appear to be problems associated with defining abnormally elevated iron levels in this context. A large number of disorders appear to be influenced by elevated iron levels, but their thresholds for predicting risk of symptomatic disease or as a signal to intervene mostly fall below the upper reference range for normal.

There appears to be a consensus that the most satisfactory approach to evaluating body iron stores or iron overload is by measuring serum ferritin rather than other serum or tissue markers for iron. However, there are significant differences in the upper limit for what is considered normal ferritin. There is also limited justification for the upper normal limits

which are typically and rather arbitrarily set at greater than the population 80th to 90th percentile. Thus there is an issue of risks associated with iron levels between the mean *or even below it* and the upper limit of normal, even when age and gender are taken into account. This actually represents a rather large range of iron stores. What is the ferritin level for any given age, gender and menopausal status that will minimize the health risks of iron in the context of such disorders as diabetes, cardiovascular, neurodegenerative or kidney disease and also cancer?

N.B. In the following discussion, all ferritin values are in the units of ng/mL.

The variation of serum ferritin levels in the US with age and gender can be obtained from the data from The third National Health and Nutrition Examination Survey (NHANES III).¹ For Caucasian men, the mean serum ferritin at age 17-19 is about 60 and by 30-39 has plateaued at about 150 where it remains until about age 60 when a steady decline to about 90 by age 90 is observed. For women, the value is quite constant at around 30 until 40 years and then after menopause rises to about 80 by age 60 and then gradually increases to about 100 at age 80-90.

Reduction of elevated ferritin levels can be accomplished cheaply and safely with blood donation, or when not allowed, by phlebotomy (blood-letting). As is well known to those who treat hemochromatosis, very large reductions in ferritin levels can be achieved without inducing anemia. The simplicity of iron stores control emphasizes the importance of defining the optimum levels and establishing targets.

FERRITIN REFERENCE RANGES REGARDED AS NORMAL

These normal ranges may appear on the lab reports returned subsequent to blood work and influence physician interpretation. There is some variation in the upper limits. Consider the following reference ranges:

- Reported by Medline (US,): Male (M) 12-300, female (F) 12-150
- Mayo Clinic: (M) 24-336, (F) 11-307
- UK: (M age 20-69) 30-400 , (F age17-60) 15-150 , (M & F age >60) 15-650
- Ontario, Canada: (M) 22-322, (F) 10-291
- According to the World Health Organization (2011), severe risk of iron overload for those age 5 or older is (M) > 200, (F) >150. Adams and Barton, in discussing the diagnosis hyperferritinemia indicate elevated ferritin levels are >300 for men and >200 for women.² One guideline for management of hemochromatosis, a hereditary iron overload disorder, indicates the normal range as (M) 20-200, (F) 15-150.³ The Iron Disorders Institute gives as the Ideal ferritin range, (M & F) 50-150.

If one looks at male population figures for ferritin levels in the US, for ages 40-59 the 50th percentile is 150 and for > 60 years it is 134.¹ For females, the corresponding levels are 53 and 86. Premenopausal women are at 32. Thus, these 50th percentile numbers representative of populations as a whole are vastly smaller than the upper limits of the normal range, which more closely corresponds to the 90th percentile numbers, for example, for US white populations from NHANES III.⁴ If this rather arbitrary approach had been used for total and LDL cholesterol, for ages above 45, the 90th percentile for men yields 266 vs. < 200 mg/dL considered desirable, and for LDL the same percentile yields 184 while 70-100 mg/dL is considered desirable. The reason is of course that data existed which convinced mainstream medicine (but not numerous critics) that risk was associated with level and studies pointed to ideal numbers much lower than the 90th percentile. The data provided below suggests that there is in fact a dependence of disease risk on ferritin levels and that the reference ranges in use may do a disservice to patients. Indeed, even the 50th percentile numbers may not be optimum.

Individuals with elevated ferritin levels and their physicians should concern themselves with possible causes. Iron overload is generally defined in terms of the degree of saturation of transferrin, which is a blood plasma protein involved in controlling the free iron in the blood. Measured as a percentage of saturation, > 50% in women and > 60% in men are regarded as evidence of iron overload. The principal cause of iron overload is either hereditary hemochromatosis or another hereditary disease called Wilson's disease. Elevated ferritin levels without iron overload can be due to liver disease, alcohol excess, and chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, or bacterial infections. Hematological malignancy may be the cause as well as an iron related cataract syndrome. In the case of this latter disorder, ferritin reduction by phlebotomy (blood-letting) is contraindicated.² Thus while there may be merits in reducing elevated ferritin with blood donation, or phlebotomy, the question of the underlying cause should not be ignored.

The issue being addressed here is when the ferritin level is below the "elevated level" or the upper limit of the reference range, and the implication regarding risk associated with disorders that are in general not responsible for the ferritin elevation and where the risk can be decreased by reducing ferritin levels.

ASSOCIATION AND THRESHOLDS OF FERRITIN LEVELS AND RISK OF VARIOUS DISEASES

- From studies in a recent systematic review, threshold ferritin levels for increased risk of incidence of type 2 diabetes were for women, 86, 107,122, 134, 150 and. For men 184,209, 215, 229, 300.⁵

- The ferritin threshold for the increased risk of any coronary calcium was >257 in a study of over 12,000 men.⁶
- In a study of men and postmenopausal women a ferritin threshold of >200 was associated with an increase in heart attack risk.⁷
- A study classified CHD-positive patients as having one or more coronary arteries with \geq 50% blockage. Comparison of ferritin levels revealed that those CHD-positive had on average ferritin levels of 121 vs. 73 for those CHD negative by this measure.⁸
- A study of ferritin levels as a risk factor for the metabolic syndrome found thresholds of >89 for premenopausal women, >212 for post-menopausal women but found no association for men.⁹
- In another study, low levels (30-42) of ferritin in premenopausal women were found to not be associated with the risk of metabolic syndrome but for postmenopausal women, a significant risk had a threshold of >52.¹⁰
- At a ferritin threshold of >137 increased risk of ischemic stroke (occlusive) was found in a study of postmenopausal women.¹¹
- A ferritin threshold of >145 to >164 was found for increased risk of acute ischemic stroke transforming to a hemorrhagic stroke in older men and women.¹²
- Inspired by the fact that iron overload can cause cardiomyopathy, a large study examined the association between ferritin levels and laboratory measured cardiovascular fitness (CVF) in young men. The likelihood of *not* having CVF, adjusted for numerous potential confounders, became significantly apparent at a ferritin threshold of >150.¹³
- Significant risk of middle-aged men developing hypertension defined as \geq 140/90 mm Hg had a ferritin threshold level > 146.¹⁴

FERRITIN THRESHOLDS FOR BENEFIT IN IRON LOWERING STUDIES

- Iron reduction in smokers with peripheral arterial disease reduced the risk of death or nonfatal heart attack such that the number needed to treat to prevent one acute event with blood-letting was only 8. The initial and final mean ferritin levels were >125 and 84.¹⁵
- In a group of patients who were either diabetic or carbohydrate intolerance, lowering mean ferritin from 272 to 45 resulted in an increase in HDL and reductions in blood pressure, triglycerides, fasting blood glucose and an improved oral glucose tolerance test.¹⁶
- A trial involving blood-letting for a group of men and women with the metabolic syndrome which decreased ferritin levels from a mean of 188 to 105 found a decrease in systolic blood pressure from 149 to 131 mm Hg with no change in a control group. Blood glucose, HbA1c and heart rate were also significantly decreased.¹⁷
- Aggressive blood-letting reduced the ferritin from 220 to 13 in patients with non-alcoholic fatty liver disease who were glucose intolerant. The result was near normalization of a serum marker for liver function and a 40-50% improvement in fasting glucose and glucose stimulated insulin.¹⁸
- Use of the oral prescription chelator deferiprone over 9 months reduced ferritin from 144 to 59 and resulted in significant improvements in patients with non-diabetic kidney disease.¹⁹
- Blood donation which resulted in ferritin levels on average decreasing from a median of 130 to 84, significantly increased HDL levels from 37 to 41 measured at 6 to 8 weeks after the last donation.²⁰
- In a trial of phlebotomy in patients with peripheral artery disease, a reduction in mean ferritin levels from a baseline of 122 to 74 resulted in a significant reduction in the incidence of visceral malignancy.²¹
- In treatment guidelines for hemochromatosis, a hereditary iron overload disorder, when phlebotomy (bloodletting) is used to lower ferritin levels, the goal is to keep levels in the 50-100 range rather than closer to the mean in the reference range applicable to the individual.³

WHAT IS THE OPTIMUM FERRITIN LEVEL?

It is clear from the above studies that the serum ferritin thresholds for the appearance of risk or the baseline values from which lowering produces benefit are mostly well below the upper reference values for normal and in fact most closely correspond to population 50th percentiles. However, the reference values are very population dependent. For example, in an elderly population in Spain consuming a variant of the Mediterranean diet, the mean ferritin levels were 107 for men and 68 for women. For individuals living in Chile, age 45-65, a threshold for risk of developing metabolic syndrome was seen in the highest quartile starting at 82. In addition elderly men from either northern Europe (Zutphen) or the Mediterranean south (Crete), had mean ferritin levels of 137 and 68 respectively. The men from Crete also had consistently lower levels of indicators of oxidative stress and higher concentrations of major antioxidants than men from Zutphen, and these differences, including ferritin, may partly account for the lower rates of CHD and total mortality observed in the Cretan cohort compared to the Zutphen group.²²

Consistent with the above data, men with ferritin levels around the population means of 130-160 are at the thresholds for disorders that are likely iron associated, but may benefit by significant lowering to below 100 and even better, that is to near the levels of iron stores depletion of about 50 for men. This latter number is in the range of that found in premenopausal women who are well known to exhibit very low rates of cardiovascular disease, differences which may not relate to estrogen.²³ Levels near the iron stores depletion values also do not in general result in anemia in men. However, premenopausal women with iron stores reduced to very low number, e.g. 10-15, are at risk of anemia.

It must be emphasized, however, that not only have the issues raised above not been specifically investigated with proper studies, but the benefits of lowering ferritin levels in asymptomatic individuals have not been investigated. Furthermore, individuals with elevated ferritin levels should realize that there are multiple possible reasons,² and that the decision to address the problem should be done under the supervision of a physician familiar with this area. The results of either blood donation or phlebotomy should be followed with particular reference to evidence for the onset of anemia. This is presumably always done at blood donation clinics, and thus frequent blood donation appears to be quite safe.

CONCLUSIONS

The normal reference ranges for ferritin span approximately the range from greater than the 5th percentile to less than the 80th to 90th percentile. As pointed out above in connection with cholesterol, this arbitrary approach is not used when the risk dependence on marker level, apparent or well established, is known. Also, it appears on the basis of admittedly limited data that the same situation exists for ferritin where the threshold for risk of a number of different disorders begins below the upper limit of the reference range, and the benefits that accrue from lowering iron stores from initial values to near or even somewhat below the 50th percentile population levels. In fact, there are enough examples of this discrepancy between practice and existing data that a case can be made for the routine measurement of serum ferritin along with blood lipids, fasting blood glucose and HbA1c, three markers that involve areas of concern and abnormal levels provide motivation for intervention. Lowering ferritin levels is noteworthy for the high level of effectiveness using blood donation which is free, safe and virtually without side effects and when disallowed by the blood donation services, can be accomplished by simple office-based phlebotomy, a procedure well established for treating hemochromatosis.

The justification for elevating "normal" ferritin to this level of clinical significance requires studies, and if justified, age-gender stratified guidelines similar to those for hypertension, fasting blood glucose and cholesterol. In the absence of sufficient evidence or a consensus, simply the recommendation of frequent blood donation represents an imperfect but practical solution. Attitudes toward vitamin D are currently undergoing this transformation from what appear to be totally unrealistic reference ranges to defined optimum, sufficiency and

deficiency levels. The really significant question is simply that for optimum health, should ferritin levels be near the bottom of the reference range, i.e. near the threshold of true body stores depletion and anemia? For many, this would require frequent blood donations, with perhaps added oral chelation if heme iron (red meat) consumption is high.

PREVENTING, SLOWING OR REVERSING CORONARY PLAQUE PROGRESSION

A recent study involved dietary advice and combined intensive lipid management (statin plus niacin) along with supplementation with omega-3 fatty acids and increased vitamin D status. The targets were triglycerides ≤ 60 mg/dL, HDL-C ≥ 60 mg/dL, and 25-hydroxyvitamin D levels ≥ 50 ng/dL (125 nmole/L). Out of 45 male and female subjects with coronary calcium scores ≥ 50 Agatston units, after about 18 months 20 subjects experienced a 15% drop in calcium score (maximum 64%), and 22 had their progression arrested or slowed to 12%, whereas a 22% to 52% increase in score per year was expected.²⁴

In another study involving hypertensive patients, a calcium channel blocker nifedipine was found to significantly slow the progression of coronary calcification when the control was a diuretic.²⁵ Lowering the triglyceride/HDL-C ratio with the drug pioglitazone was associated with a beneficial impact on the progression of coronary atherosclerosis in diabetic patients.²⁶ Low carbohydrate diets incidentally produce similar effects on this ratio. This study suggests the importance of examining the impact of addressing the dyslipidemia of the metabolic syndrome with aggressive dietary intervention with the goal of reversing coronary atherosclerosis. In a mouse study, high HDL-C was found to promote rapid regression of atherosclerosis and to alter the inflammatory properties of monocyte-derived plaque.²⁷ Potential modifiable risks factors associated with the severity or progression of coronary calcification also include physiological stress²⁸, depression²⁹ and sleep apnea.³⁰

Another recent study examined the benefits of adopting a low-risk lifestyle in the context of atherosclerosis, cardiovascular events and mortality.³¹ The data was from the Multi-Ethnic Study of Atherosclerosis (MESA) database and included coronary calcium. Four lifestyle-related variables were chosen: diet, BMI, smoking status and the level of physical activity. A binary scoring system was used – Mediterranean vs. unhealthy diet, optimal BMI vs. suboptimal, never smoker vs. ever smoker, and regular physical activity vs. sedentary lifestyle. Good diet components were vegetables, legumes, fruits, nuts cereal/grains and fish whereas unfavorable components were full-fat dairy, meat, poultry and saturated fat. These were judged against median intake and along with alcohol consumption generated a score of 0 or 1 for diet. Optimal BMI was ≥ 18.5 to ≤ 24.9 and suboptimal ≥ 25 or ≤ 18.5 . Active was defined as more than 150 minutes/week of moderate intensity physical activity or more than 75 minutes/week of vigorous activity. Thus the total score ranged from 0 to 4 based on yes or no to meeting the criteria for each lifestyle category. The follow-up was 7.6 years and the endpoints were coronary calcium incidence, progression, and all-cause mortality. The results are presented in the following table for the four lifestyle scores and the combined score of 3 and 4. Odds ratios (OR) are based on a reference of a score of 0.

**Dependence of various outcomes on the lifestyle score based on MESA data
Adapted from Ahmed *et al.*³¹**

| ENDPOINT | MEASURE | 1 | 2 | 3 | 4 | 3 or 4 |
|-----------------|---------------|----|----|----|----|--------|
| CAC INCIDENCE | RRR (%) | NS | 28 | 53 | 46 | 52 |
| CAC PROGRESSION | Δ CACS | 25 | 20 | 18 | 14 | -- |
| CHD EVENT | RRR (%) | NS | NS | 39 | NS | 37 |
| ALL-CAUSE DEATH | RRR (%) | NS | 39 | 51 | 81 | 55 |

RRR--% relative risk reduction, CACS—coronary calcium score, NS—not significant

In terms of absolute benefit, the absolute risk reductions obtained when the reference group (score 0) was compared with the score group 3 or 4 was 3.9% (NNT = 26) for all-cause mortality and 1.9% (NNT = 53) for CHD events.

The impact of combined aged garlic extract (AGE) and coenzyme Q-10 (CoQ-10) on CAC progression has also been investigated.³² In a recent study 65 individuals at intermediate risk of CHD were treated for one year with daily dose of 1200 mg of AGE and 120 mg of CoQ-10. For the treated and placebo groups in this randomized trial, the baseline CACSs were 169 and 211. The absolute change in CACS at 1 year in these two groups was 32 and 58 AU respectively. In a regression analysis adjusting for age, gender, diabetes, hypertension, hyperlipidemia, family history of CAD, smoking status and statin therapy, the odds vs. the placebo for lack of progression (< 25 AU) were almost 4-fold and statistically significant. The authors comment that these results are consistent with their earlier results with AGE alone. They also point out that AGE has been shown to improve vascular function, have a favorable effect on oxidative biomarkers and on smooth cell proliferation and the entry of lipids into arterial wall and macrophages. They list a number of additional benefits. CoQ-10 has been shown to be an antioxidant and a free-radical scavenger and has been found to be lower in individuals with CHD.

Through the generation of reactive oxygen, circulating iron has the capability of inducing considerable cellular damage and elevated iron body stores are associated with many age-related chronic diseases including CVD.³³ The fact that premenopausal women have very low ferritin levels compared to men of the same age and in addition have very low rates of heart disease has been associated with iron although this possibility is ignored or incorrectly attributed exclusively to hormones.²³

There appears to be only one study, recently published, where the association between ferritin levels, the marker for iron body stores, and coronary atherosclerosis was the issue.⁶ A group of 12,033 men underwent cardiac computed tomography in order to obtain their coronary artery calcium scores (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 4 for ferritin levels was compared with quartile 1, the odds of having a CACS > 0 associated with elevated ferritin was increased by 69% with a high level of statistical significance. This result was adjusted for confounding by using model containing all conventional risk factors.

While not measuring blood lipid profiles is tantamount to malpractice, few physicians appear to measure ferritin and presumably even fewer respond to mildly elevated levels with advice to donate blood or seek phlebotomy. Lowering ferritin levels also impacts glucose metabolism in type 2 diabetes, in fact rather dramatically, and iron generated free radicals are particularly toxic to pancreatic beta-cells. The question remains—should both men and women be below 100ng/mL with women somewhat lower than men?

MAINSTREAM MEDICINE BRINGS CANCER OVERTREATMENT AND OVERDIAGNOSIS INTO FOCUS

The subject of overdiagnosis and over treatment in modern medicine has been discussed frequently in IHN. Books such as Shannon Brownlee's *Overtreated* have been reviewed. The overdiagnosis and overtreatment of cancer is the poster child of this phenomenon, and in March, 2012 the National Cancer Institute convened a meeting to evaluate this problem, and what was termed a brainstorming session resulted in a working group which has just

presented their views in the August 28 issue of the *Journal of the American Medical Association*.³⁴

Over the past 30 years there has been growing emphasis on the early diagnosis of cancer through screening. The goal was to reduce the rate of late-stage cancer and decrease cancer mortality. The JAMA *Viewpoint* article starts by pointing out accumulated data which suggest that these goals have not been met. There has been a significant increase in early-stage disease without a proportional decline in later-stage disease. In simple terms, the complexity of the pathological condition called cancer has made it difficult in the screening process to distinguish those abnormalities which are not significant and those that would be expected to evolve into a life-threatening situation that pose a risk requiring intervention. One might say the abnormality in question is given the benefit of the doubt, declared cancer, and treated with the standard heavy artillery.

The authors divide certain common cancers into three categories.

- Breast and prostate cancer screening appear to detect more cancers that are potentially clinically insignificant and lung cancer could be included if high-risk screening is adopted. Ductal carcinoma of the breast and Barrett's esophagus are cited as examples where the detection and removal of precancerous lesions have not led to lower incidence of invasive cancer.
- Thyroid cancers and melanoma are given as examples where expanded screening has resulted in increased detection of indolent disease.
- Colon and cervical cancer are examples of effective screening programs in which early detection and removal of precancerous lesions have reduced the incidence as well as late stage disease.

In developing ideal screening programs the focus must be on differentiating indolent disease from disease that will ultimately cause harm. The authors point out the challenges associated with a better understanding of the biology of individual cancers and the disease dynamics. The writing group made the following recommendations to the National Cancer Institute for consideration and dissemination.

- The general public, patients and physicians must recognize that overdiagnosis is a common problem and occurs frequently in cancer screening. Acknowledging the consequences of screening should lead to testable approaches designed to mitigate the problem.
- The use of the term *cancer* should be reserved for describing lesions with a reasonable likelihood of progressing if not treated. Premalignant conditions such as ductal carcinoma in situ or high-grade prostatic intraepithelial neoplasm would not be called cancer or even neoplasia and the word cancer avoided altogether in discussions with patients. The proposal is to take the lowest grades of tumors, the most benign appearing lesions, and remove the word carcinoma and the stigma of cancer. Unfortunately, improved methods of making such judgements more definitive is now only work in progress and the authors provide little guidance as to overcoming the challenge of ingrained standards of practice.
- Mitigate overdiagnosis by reducing low-yield evaluations, reduce the frequency of screening, focus screening on high-risk populations, raise the thresholds for recall and biopsy, and improve the selection process of candidates for screening.
- Finally, the authors recommend research focused on the physiological and environment milieu in which precancerous and cancerous conditions arise and suggest this as potentially leading to alternatives for surgical excision.

This viewpoint is really an urgent demand for research to perfect what are now imperfect screening protocols in order to prevent the obvious harm of overdiagnosis and concomitant overtreatment. But where will the pressure originate? Perhaps from more public awareness

of the current situation described above. The *JAMA* article was reviewed by Tara Parker-Pope in the *New York Times*, and doubtless other high profile media. There may well be more and more individuals asking themselves if they were treated unnecessarily with serious if not disastrous impact on their quality of life. Thus the pressure may come from public resistance to follow the conventional pathways to surgery, radiation and chemotherapy without more evidence that it is justified and without demanding a good answer to the question of what is the risk of watchful waiting or the question, will the proposed treatment reduce the risk of developing late-stage disease or disease related mortality? At this point in time, it appears that answers that are really evidence based are not available for many cancers detected by screening. In fact, the group convened by the National Cancer Institute appears to place considerable emphasis on the need for research into this important area. One of the principal over diagnosed cancers is ductal carcinoma in situ which when diagnosed presents life threatening risk to only a small percentage of women. Identifying them now appears to be actively and urgently pursued.

NEWS BRIEFS

CALIFORNIA SETS NEW LOWER LIMITS FOR METHANOL INGESTION

Readers will recall the lead story in IHN (June 2012) that described the dangers of ingesting the artificial sweetener aspartame (Equal, NutraSweet) based on methanol being one of the products when the molecule was broken up upon digestion. The toxicity arises when methanol is converted enzymatically to formaldehyde only in certain tissues and locations, which then exerts its toxicity by reacting rapidly with components of nearby tissue. The potential to cause or rapidly accelerate most of the chronic diseases of aging was explored and documented. Simultaneous consumption of ethyl alcohol from wine, beer etc. strongly inhibits the conversion of methanol to formaldehyde and provides protection.

The State of California has now set the limit for methanol ingestion as 23 mg daily. When this is converted into dietary sources, 23 mg is equivalent to one can of aspartame sweetened diet soda, 10 cigarettes, 3 tomatoes, or 4 cans of green beans according to the prominent critic of aspartame, Rich Murray.

This is, in the view of critics of aspartame, a big step forward. The reader is referred to the above cited in the cited IHN issue for the disturbing details of the toxicity of the aspartame metabolite formaldehyde. Aspartame can be purchased by the pound in supermarkets and is present in many artificially sweetened drinks and prepared foods.

LOW-DOSE, LONG-TERM ASPIRIN AND CANCER RISK

A randomized, placebo controlled follow-up trial assigned about 40,000 women to either 100 mg aspirin every other day or a placebo.³⁵ Follow-up was for 10 years followed by 8 years post-trial surveillance. The endpoint was cancer incidence (lung, breast or colorectal) and cancer mortality. The report stratifies by overall, during trial and post-trial results. Overall there was a 20% relative risk reduction in colorectal cancer with a number needed to treat (NNT) to prevent one case of 500. The only other significant result was a post-trial 42% risk reduction in colorectal cancer (NNT 330). If one examines the cumulative incidence plots, for colorectal cancer there was no effect whatsoever for the trial period and then the difference between the placebo group developed over the additional 8 years to yield a NNT of 322. This sudden divergence should have introduced some concern regarding the design of the trial with its post-trial period. This study provides a splendid example of newsworthy relative risk reductions and yet NNT so large as to make the intervention look totally useless. Needless to say, the former was featured in the media coverage. The reader will find many similar examples on the website www.theNNT.com with commentary written by MDs.

SCANDAL OVER STUDIES CONCERNING THE BLOOD PRESSURE MEDICATION DIOVAN

The journal *Lancet* has retracted a study (the Jikei Heart Study) on valsartan (Diovan) after an investigation at the Jikei University concluded that the data on blood pressure were not reliable, and stated "We suspect that the data were altered during their statistical analysis." This follows a retraction by the *European Heart Journal* earlier this year of the Kyoto Heart Study report on this drug which had several authors in common with the Jikei Heart Study. According to *Retraction Watch*, the information provided as to the individual responsible for the statistical analysis of the Jikei Heart Study stated that the person was in the Department of Clinical Epidemiology at Osaka City University, but this was incorrect. While he had a part-time position as lecturer in the Department of Medicine, it was unpaid and he was in fact an employee of the pharmaceutical company that makes valsartan. The online cardiology website *heartwire* also points to allegations of fraud involving five papers in the journal *Circulation* and other American Heart Association journals coauthored by the Kyoto Heart Study senior author. One can only wonder how many other studies are out there influencing practice and guidelines that are also fraudulent, indicating benefits which do not exist. Another issue involves how widely disseminated the news of withdrawal becomes.

VITAMIN D REDUCES RECURRENT EAR INFECTIONS IN YOUNG CHILDREN

A study just reported at the Interscience Conference on Anti-Microbial Agents and Chemotherapy by Susanna Esposito and colleagues found that supplementation with 1000 IU of vitamin D per day significantly decreased the risk of experiencing one or more episodes of acute otitis media (ear infection) in a group of children of mean age 33 months. Vitamin D levels as measured by 25-hydroxyvitamin D were 25.8 ng/mL in the placebo group and 26.5 ng/mL in the intervention group. After 6 months, the placebo group had levels of 18.7 ng/mL vs. the treatment group at 36.2 ng/mL. Over a 12 month period prior to the study the average number of episodes was 5 in each group and one-third were complicated by perforation. During the 6 months of the study, there were 10/58 children who had one or more episodes in the vitamin D group vs. 29/58 in the placebo group. It is of interest that the conventional treatment protocol has been subject to some controversy because of the issue of the overuse of antibiotics, with recommendations from the American Academy of Pediatrics in February 2013 advocating stricter diagnostic criteria and observing rather than treating patients with uncomplicated cases. Vitamin D levels > 30 ng/mL are regarded as sufficient but the optimum level in this age group does not appear well studied. More impressive results might have been found if the treated group had reached 40-50 ng/mL.

VITAMIN D LEVELS AND BREAST CANCER IN INDIVIDUALS WITH LOW VITAMIN D STATUS

A study based on a group of women from Saudi Arabia, mean age 48 years, recently reported in *The American Journal of Clinical Nutrition*.³⁶ This case control study population was drawn from patients admitted to hospital between June and August 2009. Breast cancer cases had significantly lower levels of 25-hydroxyvitamin D (25(OH)D) than controls (9.4 vs. 15.4 ng/mL). In comparison with those in the highest vitamin category (≥ 20 ng/mL), women with 25(OH)D levels < 10 had a 6-fold increase in incidence and those between 10 and 20 ng/mL had a 4-fold increase. A level of 20 ng/mL is still not sufficient and the low levels even for a group recruited in the summer presumably reflects the darker skin type and the likelihood of reduced exposure to UV radiation associated with cultural dress practices and an indoor lifestyle.

These results are consistent with numerous studies supporting the view that women need vitamin D levels exceeding 20 ng/mL, a recommendation still seen. In fact, a study published in July 2009 in *Annals of Epidemiology* found that raising 25(OH)D levels to 40-60 ng/mL would prevent 58,000 new cases of breast cancer and three-quarters of deaths from this disease in the US and Canada. Achieving these levels with supplementation is simple and inexpensive, and emphasizes that everyone should know their 25(OH)D number.

FLOROQUINOLONE ANTIBIOTICS AND RISK OF PERMANENT NERVE DAMAGE

In 2008 The US Food and Drug Administration issued a “Black Box” warning, the highest level, for fluoroquinolones in connection with the potential to cause tendon rupture. The FDA is now requiring drug labels (package insert) and medication guides for all fluoroquinolone antibiotic drugs to better describe the serious side effect of peripheral neuropathy that may result from their use. Serious nerve damage may appear early and what is even more disturbing, may be permanent. This applies to the drug taken either orally or by injection. Approved drugs in this class include Cipro, Avelox, Nuroxin, Flosin and Factive.

It is clear from a quick examination of the anecdotal evidence on the internet that the above perhaps understates considerably the problems associated with this class of drug. There is in fact a considerable body of anecdotal evidence- based individual horror stories that might suggest that this class of drug be reserved for anthrax and other similarly critical situations. Early in the history of these antibiotics, temporarily or permanently disabling side effects were termed by the victims as being “floxed.” Unfortunately, side effects that are relatively rare but nevertheless can be very serious generally do not receive much attention, and evidence of an association with a new drug just taken is generally denied. INH readers may find Stephen Fried’s book *Bitter Pills* of interest in connection with this FDA update. Now long out of print but still available, the Fried’s book relates the life altering impact of a series of side effects experienced by his wife which followed taking one dose of a fluoroquinolone.

REFERENCES

- (1) Zacharski LR, Ornstein DL, Woloshin S, Schwartz LM. Association of age, sex, and race with body iron stores in adults: analysis of NHANES III data. *Am Heart J* 2000 July;140(1):98-104.
- (2) Adams PC, Barton JC. A diagnostic approach to hyperferritinemia with a non-elevated transferrin saturation. *J Hepatol* 2011 August;55(2):453-8.
- (3) Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011 July;54(1):328-43.
- (4) Ferritin reference levels by gender and age. www.mylaboratoryquality.com/main1x.htm? 2013.
- (5) Zhao Z, Li S, Liu G et al. Body iron stores and heme-iron intake in relation to risk of type 2 diabetes: a systematic review and meta-analysis. *PLoS One* 2012;7(7):e41641.
- (6) Sung KC, Kang SM, Cho EJ, Park JB, Wild SH, Byrne CD. Ferritin is independently associated with the presence of coronary artery calcium in 12,033 men. *Arterioscler Thromb Vasc Biol* 2012 October;32(10):2525-30.
- (7) Holay MP, Choudhary AA, Suryawanshi SD. Serum ferritin-a novel risk factor in acute myocardial infarction. *Indian Heart J* 2012 March;64(2):173-7.
- (8) Haidari M, Javadi E, Sanati A, Hajilooi M, Ghanbili J. Association of increased ferritin with premature coronary stenosis in men. *Clin Chem* 2001 September;47(9):1666-72.
- (9) Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care* 2004 October;27(10):2422-8.
- (10) Cho GJ, Shin JH, Yi KW et al. Serum ferritin levels are associated with metabolic syndrome in postmenopausal women but not in premenopausal women. *Menopause* 2011 October;18(10):1120-4.
- (11) van der AD, Grobbee DE, Roest M, Marx JJ, Voorbij HA, Van der Schouw YT. Serum ferritin is a risk factor for stroke in postmenopausal women. *Stroke* 2005 August;36(8):1637-41.
- (12) Choi KH, Park MS, Kim JT et al. The serum ferritin level is an important predictor of hemorrhagic transformation in acute ischaemic stroke. *Eur J Neurol* 2012 April;19(4):570-7.
- (13) Mainous AG, III, Diaz VA. Relation of serum ferritin level to cardiovascular fitness among young men. *Am J Cardiol* 2009 January 1;103(1):115-8.
- (14) Kim MK, Baek KH, Song KH et al. Increased serum ferritin predicts the development of hypertension among middle-aged men. *Am J Hypertens* 2012 April;25(4):492-7.

- (15) Depalma RG, Zacharski LR, Chow BK, Shamayeva G, Hayes VW. Reduction of iron stores and clinical outcomes in peripheral arterial disease: outcome comparisons in smokers and non-smokers. *Vascular* 2013 March 21.
- (16) Facchini FS, Saylor KL. Effect of iron depletion on cardiovascular risk factors: studies in carbohydrate-intolerant patients. *Ann N Y Acad Sci* 2002 June;967:342-51.
- (17) Houschyar KS, Ludtke R, Dobos GJ et al. Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial. *BMC Med* 2012;10:54.
- (18) Facchini FS, Hua NW, Stoohs RA. Effect of iron depletion in carbohydrate-intolerant patients with clinical evidence of nonalcoholic fatty liver disease. *Gastroenterology* 2002 April;122(4):931-9.
- (19) Rajapurkar MM, Hegde U, Bhattacharya A, Alam MG, Shah SV. Effect of deferiprone, an oral iron chelator, in diabetic and non-diabetic glomerular disease. *Toxicol Mech Methods* 2013 January;23(1):5-10.
- (20) van JH, Pool GF. Beneficial effects of blood donation on high density lipoprotein concentration and the oxidative potential of low density lipoprotein. *Atherosclerosis* 2002 April;161(2):395-402.
- (21) Zacharski LR, Chow BK, Howes PS et al. Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial. *J Natl Cancer Inst* 2008 July 16;100(14):996-1002.
- (22) Buijsse B, Feskens EJ, Moschandreas J et al. Oxidative stress, and iron and antioxidant status in elderly men: differences between the Mediterranean south (Crete) and northern Europe (Zutphen). *Eur J Cardiovasc Prev Rehabil* 2007 August;14(4):495-500.
- (23) Mascitelli L, Goldstein MR, Pezzetta F. Explaining sex difference in coronary heart disease: is it time to shift from the oestrogen hypothesis to the iron hypothesis? *J Cardiovasc Med (Hagerstown)* 2011 January;12(1):64-5.
- (24) Davis W, Rockway S, Kwasny M. Effect of a Combined Therapeutic Approach of Intensive Lipid Management, Omega-3 Fatty Acid Supplementation, and Increased Serum 25 (OH) Vitamin D on Coronary Calcium Scores in Asymptomatic Adults. *Am J Ther* 2009;16(4):326-32.
- (25) Motro M, Shemesh J. Calcium Channel Blocker Nifedipine Slows Down Progression of Coronary Calcification in Hypertensive Patients Compared With Diuretics. *Hypertension* 2001 June 1;37(6):1410-3.
- (26) Nicholls SJ, Tuzcu EM, Wolski K et al. Lowering the triglyceride/high-density lipoprotein cholesterol ratio is associated with the beneficial impact of pioglitazone on progression of coronary atherosclerosis in diabetic patients: insights from the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study. *J Am Coll Cardiol* 2011 January 11;57(2):153-9.
- (27) Feig JE, Rong JX, Shamir R et al. HDL promotes rapid atherosclerosis regression in mice and alters inflammatory properties of plaque monocyte-derived cells. *Proc Natl Acad Sci U S A* 2011 April 26;108(17):7166-71.
- (28) Seldenrijk A, Hamer M, Lahiri A, Penninx BW, Steptoe A. Psychological distress, cortisol stress response and subclinical coronary calcification. *Psychoneuroendocrinology* 2011 May 26;Published ahead of print May 28, 2011.
- (29) Janssen I, Powell LH, Matthews KA et al. Depressive symptoms are related to progression of coronary calcium in midlife women: The Study of Women's Health Across the Nation (SWAN) Heart Study. *Am Heart J* 2011 June;161(6):1186-91.
- (30) Kepez A, Niksarlioglu EY, Hazirolan T et al. Evaluation of association between obstructive sleep apnea and coronary risk scores predicted by tomographic coronary calcium scoring in asymptomatic patients. *Anadolu Kardiyol Derg* 2011 June 7.
- (31) Ahmed HM, Blaha MJ, Nasir K et al. Low-Risk Lifestyle, Coronary Calcium, Cardiovascular Events, and Mortality: Results From MESA. *Am J Epidemiol* 2013 June 2.
- (32) Zeb I, Ahmadi N, Nasir K et al. Aged garlic extract and coenzyme Q10 have favorable effect on inflammatory markers and coronary atherosclerosis progression: A randomized clinical trial. *J Cardiovasc Dis Res* 2012 July;3(3):185-90.
- (33) Kell DB. Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. *BMC Med Genomics* 2009;2:2.
- (34) Esserman LJ, Thompson IM, Jr, Reid B. Overdiagnosis and overtreatment in cancer: An opportunity for improvement. *JAMA* 2013 August 28;310(8):797-8.

- (35) Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-Day, Low-Dose Aspirin and Cancer Risk: Long-Term Observational Follow-up of a Randomized Trial. *Ann Intern Med* 2013 July 16;159(2):77-85.
- (36) Yousef FM, Jacobs ET, Kang PT et al. Vitamin D status and breast cancer in Saudi Arabian women: case-control study. *Am J Clin Nutr* 2013 July;98(1):105-10.



<http://www.yourhealthbase.com/vitamins.htm>

Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: <http://www.yourhealthbase.com>

ISSN 1203-1933 Copyright 2013 by Hans R. Larsen

INTERNATIONAL HEALTH NEWS does not provide medical advice. Do not attempt self-diagnosis or self-medication based on our reports. Please consult your healthcare provider if you are interested in following up on the information presented.