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William R. Ware, PhD - Editor

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Conflicts of interest and special interests have the potential for destroying the credibility of modern medicine. Manifold evidence includes the infiltration of the continuing medical education system by speakers paid by Big Pharma to give talks that may promote, perhaps in a subtle fashion, but nevertheless promote their drugs. Major high impact medical journals accept advertising for pharmaceuticals. If they need advertising revenue to stay afloat, there are many items that appeal to high earners that they could advertise, but this activity is restricted to pharmaceuticals. Journals also receive considerable revenue from the sale of reprints of clinical studies which Big Pharma needs to hand out to physicians at meetings and in their offices. Also partially supported are the many big annual meetings through among other things, paying for elaborate and frequently high-tech booths where companies attempt to convince attendees of the merits of their latest offerings and sponsoring symposia with talks that help sales. Some physicians have even been paid directly or indirectly for high prescription performance of certain drugs, and are frequently paid considerable sums to recruit patients for studies. All of this puts physicians in the position of indebtedness to a set of companies which have enriched their incomes. In addition, Big Pharma woos these professionals with lavish dinners to promote drugs and on occasion trips for the whole family when their efforts have resulted in a high level of prescriptions for some drug. While these practices may be declining, there is cause for concern.

Big Pharma has also gained significant influence on the professional specialist organizations such as all the American Medical Boards, Societies or Associations, also now called guilds. Yet the public and many physicians regard these organizations with trust and respect their guidelines, some of which are strongly industry biased and yet are all that exists.

In academia, the influence is multifactorial. Academics receive money to do studies which provide the temptation to please the sponsors, serve on various boards, and go around the country giving talks promoting a company's drugs. The latter activity is called belonging to a speaker's bureau. Clinical studies sponsored by pharmaceutical companies generally require participation of academics, frequently several, or even many, and now it is possible to examine their financial ties to the industry. The norm can be simply described as significant to extensive. It is not uncommon that individual physicians

involved in a study through a group of patients will not have access to the full set of final data, an opportunity to examine the data analysis nor a voice in the published paper, but are listed as authors and trial investigators. In extreme cases, the company does the trial and writes or farms out the writing of the paper to a company and then hires a high profile academic to act as ghostwriter whose only contribution is frequently proof reading and generating credibility concerning the results of the trial. The freedom the industry has in the design, execution and analysis of trials contributes to the loss of credibility which is greatly increased by court documents when harm from rigged trials or suppressed results end up in a lawsuit or criminal charges. The industry's image is not improved when criminal fines over just a few years add up to billions.

Regulatory agencies with the mandate of approving drugs on the basis of efficacy and safety have, in some countries, a relationship with the industry which makes pharmaceutical company clients deserving careful handling and respect for their goals, which can significantly differ from simply making and selling drugs that are safe and effective. In the US it is remarkably common that the FDA administration overrules the medical science committees and approves drugs which were not approved lower down in the chain of command.

The industry has strong influence on the media and what it can and cannot say about the above issues. This of course arises partly from huge advertising revenue since in the US (and otherwise only in New Zealand) direct to consumer advertising of prescription drugs is allowed. Count the Big Pharma ads on the US national evening news. They constitute a majority of the advertising complete with fine print and rapidly described side effects. The media thus has a huge conflict of interest and it is reflected in their news coverage. The public is deprived of news that would give them a true picture. However, there are major components of the media that do not play this game and what they report is fodder for the social media which obviously has widespread influence. This can only increase and eventually there may be a catastrophic loss of confidence among the general public in what they are being told concerning a whole host of health-related issues. The potential for loss of confidence is already being dramatically exposed in the US election drama, the Brexit phenomenon and what one hears about attitudes toward the EU in France.

This is just a very brief glimpse or a sad story of one of the weaknesses of human nature, the partial collapse of ethics, and both institutional and personal corruption, some would say a "bad apple" and "bad barrel" problem. Those wanting details and evidence, read Professor Peter Gøtzsche's book *Deadly Medicines and Organized Crime. How Big Pharma Has Corrupted Healthcare.*

Wishing you and your family a safe and healthy summer,

William R. Ware, PhD, Editor

Highlights

NEW STUDY CLARIFIES NEWCASTLE DIET CURE FOR TYPE 2 DIABETES

The Newcastle diet developed by Dr. Roy Taylor and colleagues at Newcastle University in the UK and presented to mainstream medicine in the 2012 Banting Memorial Lecture achieved what the conventional wisdom considered very unlikely if not impossible – a simple dietary intervention that cured type 2 diabetes. That is still the view of the vast majority of "experts." This significant advance was discussed in IHN in the October 2014 issue.

A second clinical study has now been published which examined both responders and nonresponders and the associated distinguishing features.[1] Thirty type 2 diabetic subjects were recruited and were given the 8-week Newcastle Diet after which they were followed for 6 months with the dietary goal of maintaining the 8-week weight loss. All diabetic drugs were stopped at the start, and baseline, end of study and 6 months data collected. Twenty-nine formed the cohort analyzed.

The subject's glucose metabolism at the start and during the study was determined by the so-called glycemic clamp technique which measures the insulin response over time to the injection by IV of a bolus of glucose. The amount of glucose then needed to maintain the elevated level provides information on beta cell function. Results from this test correspond well with the 2-hour glucose tolerance test but provide a clear picture of the insulin response of the pancreatic beta cells. Weight fell on average 14 kg (31 lbs). There were 12 responders and 17 non-responders, with the former returning to normal non-diabetic glucose metabolism which was maintained for 6 months. The interesting issue involves the characteristics of the nonresponders and in particular the baseline characteristics. The results were as follows:

- The nonresponders failed to normalize their fasting glucose or HbA1c. However, they lost and maintained the same amount of weight as responders.

- The responders had shorter diabetes durations. Responders comprised of 9/15 of the short duration group vs. 3/14 for the long duration group.
- At baseline, responders had lower fasting glucoses and HbA1c (8.9 vs 13.2 mmol/L and 7.1% vs. 8.4%.
- At baseline, responders were on less diabetes medication.
- Most significant, however, was the difference in first phase insulin response which was very large suggesting that there would have been a large difference in the 2-hour glucose challenge test (oral glucose tolerance test). Beta cell response had deteriorated to a much larger extent in non-responders.
- At the end of the diet intervention, the responders had a significant increase in first phase response vs. much lower response in the nonresponders.
- At 6 months, the responders and nonresponders had almost unchanged first phase response, maintaining the very large difference
- The responders had higher baseline plasma insulin.

The authors comment that, consistent with the study, the anecdotal feedback they received when the individuals tried the dietary approach simply from information available, avoiding weight gain appeared to be critical for maintaining normal glucose metabolism once diabetes had been cured. They also point to the critical question of how long the normal glycemia can be maintained and mention a trial underway to examine this question.

Finally, this study emphasizes the importance of the beta cell function in reversibility where for those who had lost almost all function, the 8-week very low calorie intervention was not sufficient. Also indicated is the importance of the oral glucose tolerance test. At the first sign of glucose metabolism impairment, action is strongly indicated. It follows that it is very important to pay attention to prediabetes and take action, such as this diet, rather than letting the deterioration of beta cell function progress. Many type 2 diabetics are totally insulin-dependent and still feel comfortable that their diabetes is well managed which is equivalent to having a false sense of security.

The prevalence of type 2 diabetes is shocking and growing. It should come high on the list of chronic diseases everyone should want to avoid. Mainstream medicine does not recognize cures aside from bariatric surgery for the morbidly obese, and type 2 diabetes is a progressive disease independent of so-called management. Readers who are not concerned about the threat of diabetes should consider this, and in addition read up on the comorbidities such as heart disease and heart failure or problems that destroy the quality of life before they destroy the patient through amputation of one or both feet or blindness.

BOTTOM LINE

This is an important study that complements the original study, clarifies the reasons for not responding, and emphasizes the importance of early intervention. It will predictably be a long time before such approaches as the Newcastle Diet will achieve general

acceptance. Increasing popularity of this approach will probably depend on social media. The reaction of mainstream medicine appears to be to ignore it. It is certainly not something Big Pharma wants to become an accepted therapy.

CHOLESTEROL – IS LOWER BETTER?

If an elevated biomarker is a risk factor for a disorder, the obvious intervention is to lower it. This is a simpleminded and simplistic but dominant view of human pathophysiology.

In 2004, O'Keefe *et al* published an influential paper which attempted to support the notion that optimal LDL levels were between 50 and 70 mg/dL.[2] For perspective according to the CDC the mean LDL levels in the US were about 116 mg/dL in 2008-2010 and this partly reflected drug therapy. The paper examined the total cholesterols levels of modern hunter-gatherers and got a range of 100 to 150 mg/dL which they suggested corresponded to LDL levels of about 50 to 70 mg/dL. The article argued the case for low cholesterol by citing levels in a variety of wild primates and animals, assuming that the cholesterol levels in baboons, monkeys, elephants and rhinoceros were all indicative of what levels were appropriate for humans. This makes a good cocktail party story since everyone knows that for the animals mentioned above, there is no data on their health in the context of their cholesterol. Since the wild animal argument seems rather absurd, all that can really be concluded is for some unknown reason, hunter gatherers, primates and African elephants were similar but the Inuit, wild horses and night monkeys had much higher levels. Where this really gets us in the great cholesterol debate is not clear. The paper also showed graphs of CHD events vs. LDL levels for a number of primary and second prevention trials. However, the percentage of events found among those treated is strongly dependent on the baseline risk of the population which varied considerably, rendering the argument of doubtful significance.

Since individuals taking statins experience side effects, some of which, much to the distress of the drug companies, cause them to stop taking this alleged miracle drug, there has been considerable industry interest in developing non-statin drugs to achieve the desired very low cholesterol levels. On Sunday April 3, the *New York Times* reported that at the annual meeting of the American College of Cardiology, results were presented which are bound to shake up the huge pro-statin community of practitioners and researchers. The non-statin drug was very successful not only in lowering cholesterol on average from 84 to 55 mg/dL but in addition raising HDL, the so-called good cholesterol, from an average of 46 to 104 mg/dL which is a very good level in the context of heart disease. In October 2015 after three years follow-up the drug company abandoned the trial on the grounds of futility but revealed the results at this April 2016 meeting. Of the 12,000 patients involved, 256 in the treated group compared to 255 in the placebo group had heart attacks. In addition, 434 treated and 444 placebo participants died from either heart attack or stroke. Researchers appeared dumbfounded when a 37% decrease in LDL levels to achieve levels estimated to be

present in modern-day hunter-gatherers and wild animals in fact made no difference in the standard endpoints all studies look at. While critics comment that statins in general fail to benefit 96-99% of those taking the drug for either primary or secondary prevention, in this case everyone failed to benefit and apparently no amount of statistical manipulation could expose any benefit at all.

This result is consistent with two other failed trials of drugs in the same class, and is good news for taxpayers and insurers since these drugs in question are expensive, with the one tested in this latest failed trial running $14,000 US per year.

These results are also consistent with the observation that the non-statin cholesterol lowering drug ezetimibe had never been shown to reduce heart disease risk when taken without an accompanying statin. They are also consistent with the belief that statins operate via a non-lipid lowering mechanism to produce the very small absolute risk reductions, and some cardiologists who do not believe in statins for primary prevention still use them for secondary prevention for their non-lipid lowering effects, believed to be partly or mostly anti-inflammatory.

DOES ALCOHOL INCREASE RISK OF DIABETES?

Studies have in fact shown that moderate alcohol consumption lowers the risk of type 2 diabetes but there is little information on how this depends on individual characteristics and lifestyle. A recent meta-analysis based on over 700,000 individuals has provided a clearer picture of this issue.[3] The investigators defined light consumption as 0-12 g/day, moderate as 12-24 g/day and heavy ≥ 24 g/day. For perspective, a 12-oz glass of 5% beer, a 5 oz glass of table wine, a 3 oz glass of fortified wine such as port or sherry, and a 1.5 oz glass of spirits all have about 13-14 g of alcohol. Table wine varies in alcohol content from about 12% to 15% by volume and a 5 oz glass thus varies in round numbers from 13 to 17 g. A 750 mL bottle of 15% alcohol by volume wine contains about 90 g of alcohol (the density of alcohol is about 0.8 g/ml). The alcohol is ethanol (ethyl alcohol), an important point, since there are a number of other alcohols in common use, and they are toxic.

This study examined the risk over a range of alcohol intake of 0 to 60 g/day. It was found that for both men and women, this range carried a reduced risk compared to abstinence. Graphs were what are termed U-shaped and looked like inverted and slightly distorted parabolas. For men, 20 g/day was most protective, but even at 50 g/d, the risk was less than for abstainers. For women the maximum benefit was seen at 30 g/day, an amount considered too high in general for women for reasons not associated with diabetes. Differences in benefit when moderate consumption was compared with abstinence were observed for age, body mass index, smoking status, physical activity and family history of type 2 diabetes, but the differences in risk within each category, for example current vs. never smoking, never reached statistical significance except for age. The risk of heavy consumption needs to be qualified since the definition used of ≥ 24 g is deceptive given that even 50 g/day for men was still protective (statistically

significant). This study does not provide information that allows direct calculation of absolute benefit. However, a rough estimate yields 1% to 3%. For anyone with no addiction risk associated with moderate alcohol or even slightly high consumption, then this small benefit seems worthwhile.

As has been discussed repeatedly in IHN, the issue of the safe level of consumption of alcohol by women is complex and related to prenatal effects on children, breast cancer and heart disease. Current opinion ranges for abstinence to one drink per day.

U-shaped risk curves showing protection for a diverse and unrelated set of chronic diseases at moderate alcohol consumption are remarkably common and appear to have no accepted explanation. It has been suggested that one explanation may be that beverage alcohol (ethanol) prevents the metabolism of methyl alcohol (methanol) to formaldehyde, thus preventing the highly deleterious effects of formaldehyde on organs and the vascular system. Formaldehyde is highly toxic even in small amounts and is also recognized as a carcinogen. The enzyme is localized and thus the damage from formaldehyde is localized. The U shaped curve is postulated to occur because the same enzyme is involved in the metabolism of both ethanol and methanol, but is much more active toward ethanol and thus this alcohol ties up the enzyme and prevents it metabolizing much methanol which allows time for it to be excreted. The metabolism of ethanol of course does not yield formaldehyde.[4] Exposure to methanol can arise from smoking, consuming canned and bottled fruits or their juices, canned vegetables and consuming the artificial sweetener aspartame which is 11% methyl alcohol by weight and a major source due to the heavy consumption of diet drinks. One major producer of diet drinks has just reintroduced aspartame. It is even available in supermarkets in one or two pound packages. Formaldehyde toxicity arises from cellular and DNA damage. This subject is explored in detail in a book by Woodrow Monte.[5] Monte attributes the dramatic increase over a number of decades of the chronic diseases of civilization to methanol toxicity. He is a Professor Emeritus of Nutrition at Arizona State University. See IHN June 2012 and December 2012 for a discussion of this hypothesis. It is interesting that formaldehyde outgassing from laminated flooring makes the evening news as a significant risk while the common sources mentioned above which are capable of producing much higher exposure are ignored.

NEW EVIDENCE THAT RISK OF CARDIOVASCULAR RISKS ARE VASTLY OVERESTIMATED

A study just published has examined the new (2013) American Heart Association/American College of Cardiology (AHA/ACC) calculator of the risk of atherosclerosis-associated major events, i.e. heart attack, fatal cardiovascular events, and stroke.[6] As readers may recall, this calculator (algorithm) when published in 2013 has come under considerable criticism concerning seriously overestimating these risks with the associated potential for unnecessary treatment with statin drugs. This new study is very important since it involved a large contemporary group followed from 2008 to 2013 and it was possible to examine separately patients who were not on statins,

something some have suggested as a confounding factor. The study group was made up of patients enrolled in the Kaiser Permanente Northern California health care program and comprised over 300,000 individuals, age 21 or older, with LDL in the range of 70 to 189 mg/dL. A wide range of race/ethnicity was involved, and the cohort included over 4000 diabetics. Thus the results apply to a contemporary US population with diverse lifestyles and baseline characteristics. Highly comprehensive medical records were available since the individuals obtained all their medical services through Kaiser Permanente.

The AHA/ACC algorithm is very important because it is being widely accepted and used to determine recommendations for statin treatment based on risk major events found in individuals without coronary heart disease, and for example, a 7.5% 10-year risk figured prominently in the guidelines that used this calculator. Since it has been demonstrated that the risk is approximately linear in time, the 7.5% over 10 years corresponds to a 3.75% risk over 5 years. Parameters used include age, gender, race/ethnicity, total and HDL cholesterol, presence of diabetes, smoking, family history of cardiovascular disease, and systolic blood pressure, and if hypertension and elevated cholesterol were treated. This information is generally readily available for most patients. The case for overestimation has been made with populations that range from the 1990s to more recent times, but this new study provides a much more contemporary view.

The 10-year risk was calculated for the group using the AHA/ACC algorithm after grouping the subjects in four 10-year risk ranges of < 5%, 5% to ≤ 7.5%, 7.5% to ≤ 10 % and greater than 10%. The results of the comparison with the Kaiser database are given in the table below.

***Table 1*. Cardiovascular risk predictions for non-diabetic non-statin users**

AHA/ACC 10-Year Risk Range	Kaiser Cohort Risk Observed	AHA/ACC Prediction	Overestimate of Risk (X = times)
< 5%	0.2%	1.04%	5.2 X
5 to < 7.5%	0.65%	3.08%	5.8 X
7.5 to < 10%	0.9%	4.34%	3.9 X
≤ 10%	1.85%	8.72%	4.7 X

Results for statin users vs. non-statin users were similar. Results for diabetes in general showed higher levels of risk, both observed and calculated by AHA/ACC, but the general picture remained unchanged; i.e. gross overestimation of risk best expressed in “times” rather than percentage. Current guidelines for statin treatment of diabetics do not even consider risk and regard all diabetics at high risk, but this study clearly indicates it is lower than commonly thought. These results represent gross and alarming overestimations. Yet the AHA/ACC approach is gaining popularity daily. If one consistently overestimates the chances of a horse winning a race by 5 times, that is a serious matter and one needs a new handicap method. The same applies to acute cardiovascular events, where the end of road is lifelong statin therapy with its risks, mostly yet unknown and uninvestigated, although high risk of diabetes now appears

well established, even by the standards of evidence-based medicine, as already discussed in IHN. Critics who point to Big Pharma influence on the AHA/ACC approach may indeed have a good case.

BOTTOM LINE

It can be argued that estimation of risk in this important area should be based on data from a relevant, contemporary group, and it appears that the Kaiser group, represents just that and the results are clear. If your doctor tells you your risk of an acute cardiovascular event is some alarming percent, ask where the number came from, an if it was AHA/ACC, refuse to have statin decisions made on this basis and if necessary provide the physician with the reference to this recent paper or an earlier paper dealing with the same problem.[7] Never forget that in spite of what arguments are provided, the absolute risk reduction in primary prevention of acute cardiovascular events is between 1% and 1.5% and no matter how hard the statin camp tries with trial after trial that is the result. In addition, for life extension, good luck, since the impact of statin therapy is statistically insignificant in all unbiased trials. For women, statin therapy should be a non-issue. No evidence of significant or clinically relevant benefit appears to exist. The latest meta-analysis cited in guidelines hid this result in the supplementary material.[8]This is precisely why guidelines are not stratified by gender. The primary prevention of acute events associated with the heart or brain (not including strokes caused by bleeding) is so ineffective for a given individual that it should only inspire the search for something that offers more hope to the 98-99% that don't benefit.

ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE AND STROKE

The use of daily aspirin for preventing first heart attacks or strokes, while widely adopted and allowed in the US to be promoted on TV, is nevertheless controversial. A key meta-analysis involving 95,000 individuals published in 2009 concluded that this intervention had uncertain value as the reduction of occlusive (clot) related events needed to be weighed against major bleeds, both gastric and cerebral.[9] The physicians involved with the NNT.com project found that cardiovascular events were prevented in 1 in 1667 treated, non-fatal heart attack in 1 in 2000 and non-fatal stroke in 1 in 3000. These are per year of aspirin therapy and yield one and twenty-year risk elevations expressed as a percentage elevation in absolute risk of 0.06, 0.05 and 0.03 for one year and 1.2, 1.0 and 0.6 for twenty years for the three types of event. The harm associated with bleeding was estimated at 1 in 3333 or 0.03% for one year or 0.6% for twenty years. Thus the numbers need to treat to experience benefit were comparable to the number needed to treat to harm. Based on these numbers around 99% failed to benefit and about 1% were harmed over 20 years. Furthermore, there was no benefit of aspirin therapy in connection with CVD mortality. Thus the conclusion is of uncertain net benefit as stated by the authors.

In 2016 the U.S, Preventive Services Task Force (USPSTF) issued a recommendation statement for aspirin prophylaxis for blood clot related cardiovascular events. The age

group 50-59 with a 10% or greater 10-year risk of cardiovascular disease who are not at increased risk of bleeding should start aspirin prophylaxis because the benefits outweighed the risk of bleeding by a "moderate" amount. For individuals 60-69 they indicated the risk/benefit was debatable, as it had to do with personal judgement regarding weighing the benefits vs. the risks. There appears to be no satisfactory data applying to those older than 70.[10] The abstract and the table of recommendations do not distinguish between men and women.

The first problem with the USPSTF recommendations is that they are presented as applying to a range of CVD 10-year risk starting at greater than 10%. They use the American Heart Association/American College of Cardiology (AHA/ACC) algorithm (calculator). However, as discussed in this issue of IHN, it now appears that this calculator actually overestimates risk by a factor of **4 to 5 times** what is actually observed in contemporary populations, which means that the recommendations are mostly for low risk rather than intermediate or high-risk individuals. With that in mind, consider the numbers presented to justify the recommendation. These numbers included absolute risks but are lifetime risks and thus apply to a range of time intervals. Their 50-59 and 60-69 age groups have life expectancies of 25 and 20 years according to recent life table whereas in many studies risk reductions are given for 5 or 10 years. In comparing with the 2009 meta-analysis, this must be taken into account. The following table gives the results for absolute lifetime risks. Absolute lifetime risks were calculated from the given events per 10,000 individuals.

Table 2. Absolute **lifetime** risk decreases for non-fatal heart attack or stroke or increases in risk of bleeds associated with daily prophylactic aspirin therapy for individuals with AHA/ACC 10-year risk of 20% for an atherosclerosis associated event. Given as percentages of individuals experiencing events.

Gender	Age	Non-Fatal MI (%)*	Non-Fatal Stroke (%)**	Gastro Bleed (%)
Male	50-59	2.9	0.92	2.5
Male	60-69	2.4	0.84	2.7
Female	50-59	1.5	1.4	1.8
Female	60-69	1.1	1.3	2.2

**** MI – heart attack ** Only strokes due to clots***

It would appear from the data above taken from the USPSTF paper which was presented in their tables, that the benefit for heart attack prevention is comparable to the risk of a gastrointestinal bleed and that this adverse risk exceeds the stroke prevention benefit in the 50-59 year age group, the age group for which definite recommendation of aspirin therapy was advanced as well as in the 60-69 age group for both men and women. Similar results are seen in the results for the 10% and 15% 10-year CVD risk levels also presented by in the USPSTF report. In connection with primary stroke prevention, a recent study from Japan found for the age group 60-85,

aspirin did not show any statistically significant benefit for risk reduction. Age > 70 years, smoking and diabetes were risk factors for stroke regardless of aspirin treatment.[11]

The USPSTF also considered the benefits in the context of colorectal cancer since aspirin is known to reduce the risk of this disease. The absolute lifetime cancer risks were smaller than the risks of gastrointestinal bleeds so the same arguments apply.

Some would argue that a gastrointestinal bleed is to be preferred to a heart attack, stroke or colorectal cancer. However, it must be kept in mind that all of these numbers are averaged over large groups of individuals and must be considered with caution when a single individual is making a risk/benefit decision. Furthermore, the absolute risks we are confronted with are small even though they apply to a long interval of time. To roughly estimate 10-year risk from lifetime risk in this age-group, divide by 2, which makes the absolute risks even smaller, and recall that a 1% absolute risk reduction means that 99% of individuals treated fail to benefit. It can be argued that when the absolute benefit is very small, the probability of a significant influence on confounding goes up and the actual benefit may actually be close to zero.

BOTTOM LINE
As is so frequently the case, attempts at primary prevention with pharmaceutical or even over the counter drug intervention results in a small absolute benefit leading to concern over absolute risks of adverse events and encourages one to seek something better than is being conventionally offered. This overall picture is also a sad commentary on the state of primary prevention in chronic diseases since it is so very common.

IRON OVERLOAD – LIVER CANCER AND NON-ALCOHOLIC FATTY LIVER DISEASE

In the July-August 2013 IHN the importance of body iron load on the prevalence of diabetes and coronary heart disease was featured. Included in this issue is an annotated manuscript written by your editor and published in *The Journal of Orthomolecular Medicine* which examined the risks of iron levels measured as blood ferritin, which were in the normal range according to conventional reference ranges. The article not only discusses the increase in the risk of a number of disorders but also the decrease in risk when the levels were lowered either by chelation or blood donation or the equivalent in blood removal. In this issue we will briefly look at the impact of iron levels on both non-alcoholic fatty liver disease and liver cancer of viral origin.

Ferritin is a large molecule which encapsulates iron and is a major factor in iron storage in the body. Some ferritin circulates in the blood and can be used as a surrogate marker for total ferritin and body stores. Elevated iron can be dangerous due to the production of highly reactive species that can produce oxidative stress, damage cells, cause DNA, organ and vascular damage. While this is well established it appears to be mostly

ignored by mainstream medicine given the very high upper limits seen in most reference ranges for blood ferritin which in fact is rarely measured in routine physical exams. Rather, the focus is on anemia which also of course has its risks. However, low body stores as reflected in low blood ferritin levels generally do not imply anemia.

Chronic liver disease can be related to hepatitis B and C viral infections and this can in turn lead to what is called hepatocellular carcinoma (HCC) or in simple terms, liver cancer. A recent case-control study, which compared 141 HCC cases and 240 patients having only chronic hepatitis B or C infections, looked at the risk associated with variable ferritin levels and correcting for age, gender, alcohol and tobacco consumption and coffee drinking. The ferritin levels were either divided in to four groups (quartiles) or into three groups termed low normal, high normal and high. The ranges are of interest:

Quartiles with ferritin in ng/dL: 2.9--39.3, 39.4--103, 104--270 and 273—3126

Male groups A, B and C: 22—109, 111—273, and 281—3126.
Females groups A, B and C
HCC study 6.2—44, 47—200 and 208—1900

Reference ranges vary according to who formulates them and where they apply. The upper limits are what are important.

- Reported on 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 age 17-60) 15-150
- Ontario, Canada, from laboratory reports: (M) 22-322, (F) 10-291
- Adams and Barton,[12] when discussing the diagnosis hyperferritinemia (the disorder of elevated ferritin) indicate elevated ferritin levels are >300 for men and >200 for women.

The study results for enhanced HCC risk by group corrected for confounding the odds of getting HCC were for A vs. B of about 3 times, and for A vs. C over 8 times. When viewed in terms of the quartiles, the risk odds vs. Quartile 1 as a reference were 5.8 for Q2, 11.75 for Q3 and 33.8 for Q4.These are obviously large and potentially serious increases in risk. Thus it is clear that many individuals with blood ferritin levels in the normal reference ranges had strongly elevated risk of developing HCC if they already had chronic hepatitis B or C.

The authors suggest the importance of measuring ferritin in the case of chronic liver disease and that iron supplements, iron-rich foods and iron-fortified foods should be avoided. However they do not suggest actively lowering ferritin, which is easily and rapidly accomplished by blood donations or “bloodletting” also called phlebotomy and even oral chelation.

For non-alcoholic fatty liver disease, there have been a number of studies recently finding an association with blood ferritin levels. To summarize:

- Vascular damage is associated with elevated ferritin levels and iron depletion shown to decrease the formation of atherosclerosis.[13]
- Elevated blood ferritin levels were also positively associated with liver fat.[14] as well as with lower insulin sensitivity and pancreatic beta-cell function.
- Two studies found elevated ferritin levels correlated with the severity of the fatty liver disease.[15, 16]
- Severity of pediatric non-alcoholic fatty liver disease correlated with blood ferritin levels.[17]
- It has also been shown that inflammation, commonly associated with elevated ferritin levels, is not the cause of high levels in non-alcoholic fatty liver disease as measured by sedimentation rates, C-reactive protein or grade of liver inflammation, even when ferritin levels were lowered by phlebotomy.[18]

The point is that in these studies the ferritin levels in question mostly fell within the normal reference ranges. See the following journal article for more information on this subject.

Solving the problem of ferritin levels judged to be unsatisfactory is relatively simple. Remove some blood or use an iron chelator to accomplish the same thing. Unfortunately, in some if not many jurisdictions, most physicians including general practitioners, family physicians and internists are not allowed to engage in phlebotomy, some blood donation services have age limits, and anyone testing positive from a serological test for hepatitis is excluded from donation. Thus while withdrawing blood offers a simple solution to elevated ferritin levels, for many it may not be possible to arrange. Referral to a haematologist will not work either since most elevated ferritin levels that may present health risks are not high enough for haematologists to justify phlebotomy or even to be regarded with cause for much concern. When confronted with this situation, oral chelation may provide a good solution, either with prescription iron chelators or combinations of supplements that appear to be equivalent. (See following article).

BOTTOM LINE

The above studies reinforce the position taken in the earlier IHN discussion and in the attached journal article. It is time for ferritin to be routinely included in health assessments and it can be argued that it is probably more significant than for example cholesterol which is almost always included in blood tests ordered for a check-up. Furthermore, the reference levels used to interpret the observed blood ferritin level obviously need to be reconsidered. This position is strengthened by the ease of lowering iron body stores and the general health merits of blood donation. The blood donation services can generally be depended upon to protect donors against donation-induced anemia.

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RESEARCH REVIEW

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

by William R. Ware, PhD

While iron is an essential element involved in many biological processes, it is also well known to be a source of reactive oxygen species trough the Fenton reaction, and the result can be oxidative stress and cellular, DNA, vascular and organ damage. Iron is bound mostly by haemoglobin and ferritin and serum ferritin levels are generally regarded as a measure of body iron stores even though serum levels constitute only a small fraction of total ferritin. Ferritin is involved in iron homeostasis and appears also to be a marker for reactive iron even though the iron it sequesters is not reactive. The currently used laboratory reference range for normal serum ferritin typically covers from the 5th to the 80th or 90th population percentile and is gender dependent. However, there is considerable evidence that within this range adverse effects of iron are implicated which impact the development and progression of a number of common disorders. There is also considerable data indicating that lowering ferritin levels within the normal range to values corresponding to near iron depletion produces beneficial results for a number of diseases. In addition, oxidative DNA damage is strongly and significantly associated with ferritin levels within the normal reference range with no apparent threshold. It is hypothesized that optimum ferritin levels are at the low end of the normal reference range near the threshold for anemia. Failure to measure ferritin and respond to results above this suggested optimum may do a disservice to patients. Either blood donation or phlebotomy is very effective in achieving these levels.

INTRODUCTION

It is well known that both low and high iron levels raise a number of health issues. Elevated iron levels can be dangerous due to the production of highly reactive species that can produce oxidative stress, damage cells and cause DNA, organ and vascular damage (Fenton chemistry). Thus the postulated association with the chronic diseases such diabetes, cardiovascular disease, the metabolic syndrome, and chronic kidney and liver disease.[1, 2] Elevated iron levels are also implicated in aging and neurological problems.[3, 4] However, there is a key issue. What constitutes significantly elevated levels?

Humans possess essential iron-handling processes for uptake, export, serum transport, and storage.[5, 6] The cellular cytoplasm contains variable amounts of highly reactive free iron, known as the labile iron pool (LIP). The LIP is thought to be composed of Fe(II) and Fe(III) weakly bound to phosphates, organic acids or glutathione. Ferritin is also present in the cytoplasm, storing iron when it is plentiful and releasing it to the LIP when needed. Ferritin is a large, hollow macromolecule built with two proteins. A complex regulatory system controls its biosynthesis.[7] It oxidizes Fe(II) and sequesters the Fe(III) in its cavity in large amounts, thus rendering the iron inactive. Thus while stored iron is

regarded as unreactive, the sequestering and secreting actions give ferritin a central role by interacting with the LIP and thus the pathophysiology associated with reactive iron.

While many of the fundamental biological aspects of ferritin are still unclear,[8] is generally acknowledged that serum ferritin levels are an important marker for iron body stores in healthy individuals. It is second only to hemoglobin in the amount of bound iron. Ferritin is versatile macromolecule having not only a role within the cytoplasm involving iron homeostasis, but may act both as an anti-oxidant and pro-oxidant. In addition, ferritin is involved in other functions related to inflammation, cellular and neurological development and angiogenesis. Serum ferritin, which represents only a small fraction of total ferritin, appears to be a marker for levels of active iron.[8, 9]

The multiplicity of physiologic processes involving ferritin and in particular, its role as an acute phase reactant, has caused some to question the use of serum ferritin as a marker for the risk of various disorders.[10, 11] However, as will be discussed, risk of incidence of various disorders correlates with ferritin levels in a large number of studies with significant numbers of participants and a diversity of disorders suggesting that this may not be a serious confounding factor. More importantly, there are also a number of disorders where lowering "normal" ferritin by blood removal from above, near or even below the population mean to *near iron depletion* (threshold for anemia) produces significant improvements in clinical manifestations and markers. This reinforces the hypothesis of iron as a potentially causal factor with serum ferritin acting as a reliable marker of available reactive iron.[12]

Humans have no regulatory mechanism for the excretion of iron in excess of what is appropriate for normal physiological processes. Thus dietary intake, especially heme iron, can cause a gradual increase in stored iron. Premenopausal women have a mechanism for iron loss (approximately a liter per year) that maintains ferritin levels significantly below that of men, but after menopause the levels approach but rarely equal that of older men.

In sharp contrast to blood lipids and measures of glucose metabolism, ferritin does not appear to be a common marker included in the set of blood tests normally ordered in the typical clinical setting. Furthermore, there is limited justification for the upper normal limits which are typically and rather arbitrarily set at the population 80th to 90th percentiles. There are in fact legitimate questions concerning risks associated with iron levels between the mean *or even below it* and the upper limit of normal, and there are a number of studies where a threshold is observed within the normal reference range above which risk of a disorder becomes significant. In addition, and what is probably more important, there is an equally large body of data indicating significant benefit accruing from lowering ferritin levels starting at levels near the upper reference range value all the way to well below the mean population value and ending at close to the onset of anemia. These data allow a critical appraisal of current reference levels and what in fact might be optimum levels.

NOTE: In what follows, the units for ferritin, ng/mL, will be omitted

FERRITIN LEVELS AND REFERENCE RANGES REGARDED AS NORMAL

There is some variation in the upper reference limits for ferritin which constitute the thresholds for concern. Consider the following reference ranges:

- Reported on 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 age 17-60) 15-150
- Ontario, Canada, from laboratory reports: (M) 22-322, (F) 10-291
- Adams and Barton,[13] when discussing the diagnosis hyperferritinemia indicate elevated ferritin levels are >300 for men and >200 for women.

The variation of serum ferritin levels in the US with age and gender can be obtained from the Third National Health and Nutrition Examination Survey (NHANES III).[14] For Caucasian men, the mean serum ferritin at age 17-19 is about 60 and by age 30-39 has a plateau 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 after menopause and then increases to about 80 by age 60 and then gradually increases to about 100 at age 80-90. These means or 50th percentile numbers representative of populations as a whole are considerably smaller than the upper limits of the normal range given above, which more closely corresponds to the 90th percentile for white populations from NHANES III.[15] 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 pointed to graded risk throughout the range of population values.

Ferritin levels 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.[16] Furthermore, in a comparison of elderly men from either northern Europe (Zutphen) or the Mediterranean south (Crete), the mean ferritin levels were 134 and 70, respectively. The men from Crete also had consistently lower levels of indicators of oxidative stress, higher antioxidant capacity and higher concentrations of major antioxidants than men from Zutphen. These differences, including ferritin, may partly account for the significantly lower rates of coronary heart disease and greater longevity observed in the men in Crete compared to those from Zutphen.[17]

Iron overload is generally defined in terms of the degree of saturation of transferrin rather than the value of serum ferritin. 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 rarely Wilson's disease. An imbalance between intake and excretion is a common cause of elevated ferritin levels without iron overload but can also be associated with liver disease, alcohol abuse and chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, bacterial infections, or iron related cataract syndrome. In the case of this latter

disorder, ferritin reduction by phlebotomy is contraindicated.[13] Elevated ferritin levels are found in the sera of many cancer patients, and higher levels correlate with poor clinical outcomes.[18]

The data provided below suggests that there is in fact an association of the risk of developing a number of disorders and ferritin levels, and that the reference ranges in use ignore this. Indeed, even the 50th percentile numbers may be far from optimum. In the studies reviewed below, most of the thresholds for risk are obtained from the ferritin levels in the quartile or quintile where odds ratios reached statistical significance.

ASSOCIATION AND THRESHOLDS OF FERRITIN LEVELS AND RISK VARIOUS DISEASES

- From five studies in a recent systematic review, threshold ferritin levels for increased risk of incidence of type 2 diabetes (T2DM) were for women 86, 107,122, 134, 150 and for men 184,209, 215, 229, 300.[19]
- A study with a 17 year follow-up found in men aged 42 to 60, the risk for T2DM began to markedly increase at a ferritin level of 185.[20]
- The ferritin threshold for the increased risk of any coronary artery calcium was >257 in a study of over 12,000 men.[21]
- In a study of men and postmenopausal women, a ferritin threshold of >200 was associated with an increase in risk of a first heart attack.[22]
- A study classified CHD-positive patients as having one or more coronary arteries with ≥ 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.[23]
- A study of ferritin levels as a risk factor for developing the metabolic syndrome found a threshold of 212 for postmenopausal women.[24]
- At a ferritin threshold of >137, increased risk of ischemic stroke was found in a study of postmenopausal women.[25]
- 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.[26]
- 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 *the* absence of CVF, adjusted for numerous potential confounders, became significantly apparent at a ferritin threshold of >150.[27]
- Significant risk of middle-aged men developing hypertension, defined as systolic BP ≥ 140/90 mm Hg, had a ferritin threshold level > 146.[28]
- A study of the relationship between increased ferritin, oxidative stress and insulin resistance in 151 healthy men revealed no threshold, only continuous increases in markers with ferritin levels from the first tertile (≤97) to the third (≥180). The correlations remained strong and significant after adjustment for inflammation.[29]

While there is admittedly the possibility of confounding in some of the above associations, the ferritin lowering studies below suggest otherwise.

FERRITIN THRESHOLDS FOR BENEFIT IN IRON LOWERING STUDIES

- In a randomized prospective trial, iron reduction in male smokers with peripheral arterial disease (PAD) reduced the risk of death or nonfatal heart attack such that the number needed to treat to prevent one acute event with phlebotomy (from Kaplan-Meir plots) was only 8 over 5 years, a very low number rarely encountered in clinical studies. Significant benefits were also seen for all-cause mortality, non-fatal MI and stroke. The initial and final mean ferritin levels were 125 and 84. In a larger study in which the above was imbedded, unequivocal benefits were found for iron reduction in younger individuals 43-61 years of age for all-cause mortality, non-fatal MI and stroke when phlebotomy reduced ferritin levels to < 70.[30, 31]
- In a group of patients who were either diabetic or carbohydrate intolerant, 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.[32]
- A controlled trial involving phlebotomy which decreased ferritin levels from a mean of 188 to 105 for a group of men and women with the metabolic syndrome, 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.[33]
- Use of the oral prescription chelator deferiprone over 9 months in patients with non-diabetic kidney disease reduced ferritin from 144 to 59 and resulted in significant clinical improvements.[34]
- In a trial using phlebotomy in patients with peripheral artery disease, a reduction in mean ferritin levels from 122 to 74 resulted in a significant reduction in the incidence of visceral malignancy.[35]
- In a study of 10 healthy individuals with initially low ferritin, 500 ml withdrawal of blood resulted in a drop on average levels from 75 to 38 and a significant improvement in the results of a glucose tolerance test one month later.[36]

Comparison of both the above thresholds for risk and the baseline ferritin levels from which lowering produced benefit reveals an inconsistency with the commonly used reference range values regarded as normal. This illustrates the major point of this review. Even when the baseline ferritin level is a below the population mean, significant benefit still derives from phlebotomy. The upper reference range values for normal appear way too high, and in fact, the above results suggest that the 50th percentile numbers are also too high. Some of the studies presented below reinforce this latter observation, leading to the hypothesis that *the lower the better* may be a justifiable goal as long as lowering does not induce anemia.

IRON STORES REDUCTIONS AND DIABETIC COMPLICATIONS

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.[37] Studies on humans are limited. A 9-month study on T2DM using deferiprone, an oral iron chelator, reduced ferritin levels from 144 to 59 and decreased the mean albumin/creatinine ratio from 187 to 25 mg/L.[34] 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 of 18% in the incidence of serum creatinine doubling [*marker for kidney problems*] and an absolute decrease of 18% in both mortality and end-stage kidney disease (number needed to treat over 4 years for either was 6).[38] Iron chelation due to the polyphenols in the diet was probably partly responsible for reduced ferritin from 325 to 53 and the benefits observed.

IRON REDUCTION AND NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) starts with simple hepatic steatosis and can progress to non-alcoholic steatohepatitis (NASH). One hypothesis for the pathogenesis of this disorder is the so-called two-hit model where the first hit involves insulin resistance, visceral obesity and increased hepatic steatosis. The second hit involves one of a number of possible insults which lead to increased oxidative stress and liver inflammation. The increased deposition of iron as the disorder progresses suggests it is involved in the second hit, given its role in producing ROS as well as other pathogenic effects including altered insulin singling and lipid metabolism. Iron may also be involved in the initial development of steatosis.[39] High ferritin levels (threshold of 1.5 X upper limit of normal or 450 for men, 300 for women) has been found independently associated with advanced hepatic fibrosis.[40] The following iron depletion studies are thus of interest.

- The effect of phlebotomy on insulin resistance in a group of patients with NAFLD and strongly elevated ferritin levels found a significant reduction in insulin resistance (HOMA-IR decreased from 4.81 to 3.12) when ferritin levels were reduced from 438 to 52. Aniline transaminase (ALT) decreased from a mean of 58.1 to near normal 34.3 IU/L [*important blood marker for liver function*].[41]
- A study examining the effect of phlebotomy involved 42 type 2 diabetic or carbohydrate intolerant subjects including 8 also diagnosed with NAFLD based on elevated ALT and ultrasound evidence of steatosis. DNA testing was used to exclude patients with hemochromatosis. The NAFLD and non-NAFLD groups had baseline mean ferritin levels of 299 and 220 respectively. Phlebotomy produced near iron depletion (ferritin 31-15) and ALT fell from 61 to 32 IU/L [*i.e. return to normal liver function*] in the NAFLD group whereas there were insignificant ALT changes observed in the NAFLD-free group. Favourable metabolic changes associated with ferritin declines were seen in fasting insulin and the oral glucose tolerance test even though there were no changes in medication. Stronger effects were observed in the NAFLD group.[42]
- In a study where ferritin levels were manipulated with diet, 12 patients with NASH were placed on a calorie, fat and iron restricted diet. Baseline mean ferritin levels were 280 initially and 128 at 6 months of intervention. ALT levels decreased from 104 to 42 IU/L over the same period. Large [*beneficial*] changes were also seen in aspartate aminotransferase (AST) levels. Both males and females had similar baseline ferritin levels, which means that the women had on average ferritin levels above the gender specific upper limits of normal, but not by very much.[43]

IRON AND OXIDATIVE DNA DAMAGE

Urinary 8-hydroxydeoxyguanosine (8-OHdG) is a reliable and frequently used biomarker of systemic oxidative DNA damage [*lower the better since high levels indicate adverse DNA damage*].[44, 45] Given such a marker, the obvious question concerns correlation with body iron stores. Two studies have addressed this important question.

Hori *et al* [46] studied over 500 healthy Japanese aged 21-67. The correlations between 8-OHdG and ferritin measured by Spearmen rank correlation coefficients were 0.47, 0.76 and 0.73 for men overall, women aged less than 50 and women 50 years or older, respectively. These strong correlations were essentially unchanged after adjustment for potential confounders. Subjects exhibited ferritin levels from near iron depletion to around 300 for men and 100 for women.

An earlier study by Nakano *et al*[45] found similar results. In a study of over 2500 healthy individuals age between 22 and 89 that there was a smooth, almost linear 2.5 fold increase in 8-OHdG for men as ferritin ranged from 10 to about 300. For women, 8-OHdG was increased by a factor of 3 for ferritin levels ranging from below 9 to 160.

These results suggest no threshold and are consistent with a study of vascular function where when two groups, both with low ferritin levels (52 vs. 17), were compared, flow mediated vascular dilation was significantly greater in the very low ferritin group.[47] It is also consistent with the study described above where ferritin levels correlated with oxidative stress and insulin resistance with no apparent threshold.[29]

These are very important results since they not only indicate a strong dependence of DNA oxidative stress on ferritin levels as a marker for active iron, but the ferritin levels span the entire reference range for normal and these were healthy individuals. Thus throughout the normal reference ranges for both genders, iron as measured by ferritin appears to be a continuously increasing risk factor for DNA damage. It is also highly significant that the threshold for iron associated DNA damage appears to be just above the level of near iron depletion level.

Two related studies are of interest. In one, lowering ferritin with phlebotomy has been found to reduce 8-OHdG in patients with chronic hepatitis C. The mean ferritin level was 259 at baseline and after phlebotomy, dropped to around 10 at 4 months and was 7.1 at 6 years. At 4 months, 8-OHdG as measured by two methods dropped to half the baseline value and at 6 years corresponded to that of normal controls. At and after about 1.5 years, ALT levels were normalized.[48]

A second study from this research group examined the impact of reducing iron stores to a near depletion on the development of hepatocellular carcinoma (HCC) from chronic hepatitis C.[49] At baseline the mean ferritin level was 371 (range 77-1180). Phlebotomy reduced iron levels rapidly to < 11 and it was held at near this value for 12 years. The incidence of HCC in the phlebotomy group was 11.4% whereas in a control group it was 32.5%. This yields a number needed to treat to prevent over 12 years one progression to HCC of 5.

WHAT IS THE OPTIMUM FERRITIN LEVEL?

It is clear from the above studies that the serum ferritin thresholds for the appearance of risk and the baseline values from which lowering produces benefit are mostly well below the upper reference values for normal and in fact more closely correspond to population 50th percentiles. However, lowering ferritin to levels far below the 50th percentile population values produces benefit associated with severity of disorders which can be influenced by iron. In some studies, this is observed even when the baseline level for lowering is already quite low. Furthermore, low ferritin levels indicating benefit achieved by phlebotomy are in the range of that found in premenopausal women who are well known to exhibit very low rates of cardiovascular disease, differences which in fact may not related to estrogen, as is commonly believed.[50] The DNA oxidative stress studies strongly support the view that the optimum ferritin level is that representing near iron depletion.

Overall, the answer to this question appears to be lower the better, provided anemia is not the result. This observation urgently needs detailed study with controlled long-term follow-up studies. It challenges two widely held beliefs, namely that ferritin anywhere in the normal reference range should not cause concern and that normal means no enhanced risk from active iron. The evidence that this is wrong appears in fact to be compelling.

INFLUENCE OF BLOOD DONATION OR PHLEBOTOMY ON FERRITIN LEVELS

Blood donation [*phlebotomy*] typically removes 450-500 ml per visit. Phlebotomy sessions are generally similar. A frequently cited number is a 30 ng/mL decrease in ferritin per donation. The following table illustrates this in a large sample of Danish men.

Danish study of the influence of blood donation of serum ferritin levels (ng/mL) in men, 30-66 years of age.[51]

Donation History Per Year	Ferritin Median	Ferritin Range (5-95 PCT)*
0	137	46-396
2	44	17-122
3	38	14-110
4	31	12-91

**** 5th to 95th percentile for given result***

The results for zero donations is similar to modern results and on average 3 to 4 donations per year will result in a ferritin level below 100 with a median representing near iron depletion.

CHELATION, THE ALTERNATIVE TO PHLEBOTOMY OR BLOOD DONATION

Oral chelation has been a common approach to iron overload for patients having pathological levels, and several prescription drugs are available, but these are not

without side effects.[52] However, ferritin levels involved in most of the studies discussed above are nowhere near those encountered in pathological iron overload. Iron lowering therapy for hemochromatosis is generally initiated at a ferritin level of 1000.

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.[53, 54] Green tea polyphenols,[55] silymarin (silybin, milk thistle extract),[56-59] and quercetin[60-62] all have documented success in iron chelation. These chelators also act to eliminate other toxic metals, although for mercury it may help to add selenium and alpha-lipoic acid to N-acetyl cysteine, but the evidence is anecdotal.[63] Curcumin was recently found to be a very good iron chelator.[64] A randomized controlled trial demonstrated the effectiveness of curcumin in significantly improving markers of glucose metabolism in T2DM, possibly partly due to iron chelation.[65] However, clinical studies to directly examine application of natural oral chelation in this context appear non-existent. The extent to which these oral chelators remove desirable or essential minerals also appears unknown, but caution and supplementation would appear prudent.

CONCLUSIONS

The reference ranges for normal ferritin levels span approximately the range from greater than the 5th percentile to less than the 80th to 90th percentile. This arbitrary approach is not used when the risk dependence on marker level is believed to be well established. It has been show that the threshold for risk for a number of difference disorders begins considerably below the upper normal limit of the ferritin reference range, and benefits accrue from lowering ferritin from initial values, frequently in the range of average or lower, to very low final values.

It appears that ferritin screening can be justified. Lowering ferritin levels can be accomplished with a high level of effectiveness by blood donation, which is free, safe, has monitoring for anemia and is virtually without side effects. When disallowed by the blood donation services, ferritin lowering can be accomplished by office- or clinic-based phlebotomy.

This review suggest the hypothesis that optimum adult serum ferritin levels in the context of health issues may be in the range of 20-40 for women and 50-70 for men. Adequately powered studies are needed to address this issue in the context of the chronic diseases where the existing studies are mostly too small and in some cases inconsistent.[2] However, examining this hypothesis would be lengthy, costly, and unlikely to find support from the pharmaceutical industry. An alternative but not ideal start would be retrospective studies based on large managed care data bases merged with blood donor clinic data due to the absence of historical ferritin data. Catchment areas are generally small enough to make this possible. Data collection would include current serum ferritin levels and other pertinent current data presumably available as well as complete medical and even prescription history. Large cohorts would be necessary to capture a significant number of individuals with consistently frequent donation. The consistently positive results obtained with phlebotomy will no doubt

encourage more and better intervention studies, which could considerably enhance the evidence base.

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