DIOS: dysmetabolic iron overload syndrome

Iron Overload different from classic hemochromatosis

Key words: hyperferritinemia; iron overload; hemochromatosis; neurodegenerative diseases; HFE; C282Y, H63D, S65C; cholesterol, triglycerides, glucose, uric acid, insulin, blood pressure; body fat; fatty liver; obese; overweight; metabolic syndrome

It is well established that moderately elevated body iron is associated with chronic disease and premature death. Nearly 16 million Americans have some degree of iron overload by inherited or acquired means.

Depending upon the degree and cause of iron overload, the consequences can include bone and joint disease, liver disease including cancer, cirrhosis, fatty liver, metabolic syndrome, cardio-vascular disease or heart failure, diabetes mellitus, hypogonadism, impotence, infertility, hypothyroidism, abnormal adrenal function, increased infection, hearing and vision loss, skin color changes (bronze, gray-green or reddish color), depression, or suicidal tendencies. Elevated iron increases risk for earlier onset of symptoms for neurodegenerative diseases: Alzheimer's disease, Huntington's, or Lou Gehrig's disease; and excess iron is prominent in areas of brain with multiple sclerosis lesions. Having mutations of the *HFE* gene, increases the risk of iron overload and these consequences.

HFE is the gene for classical hemochromatosis (type I) hemochromatosis, a leading cause of iron overload disease. Mutations of HFE occur in a variety of patterns, the most at risk are those who are: C282Y/C282Y or H63D/H63D (homozygotes) or C282Y/H63D (compound heterozygotes). Another rare mutation S65C is believed to cause less severe iron overload. Hereditary hemochromatosis type I (HHC) is very common in the white population; about one million Caucasians in the USA have the C282Y/C282Y inheritance pattern—as many as four million have other *HFE* inheritance patterns of hemochromatosis. When people appear "tan" without being in the sun or early deaths due to heart or liver failure, or where there is a history of suicide often undetected hemochromatosis will arise as suspect by people knowledgeable about the disease. Some think that the suicide, alcoholism and depression of Ernest Hemmingway and the cirrhosis experienced by Beethoven were due to hemochromatosis.

HHC is characterized by serum transferrin-iron saturation percentage (TS%) above 45% (fasting), accompanied by an elevated serum ferritin above 200ng/mL in adult females or 300ng/mL in adult males. When these patients are diagnosed before serum ferritin is above 1,000ng/mL and they undergo successful iron reduction (phlebotomy or blood donation), the risk of liver damage is less than 1% and they can expect normal lifespan. When serum ferritin is allowed to rise above 1,000ng/mL the risk of serious, irreversible organ damage increases 20-200 fold! For this reason alone, early detection and treatment of iron overload are imperative.

More recently, a condition called dysmetabolic iron overload syndrome (DIOS) is described. DIOS also results in mild iron loading, but unlike classic hemochromatosis, it is characterized by normal TS% with elevated serum ferritin.

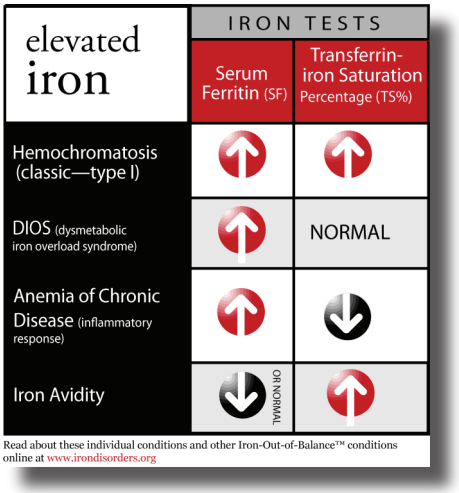
Generally, people with DIOS have elevated levels of blood pressure and serum cholesterol, triglycerides, glucose, uric acid, insulin. These individuals are likely to have mildly elevated liver enzymes, especially GGT and have a fatty liver. Two-thirds will have elevated urine levels of hepcidin. People with DIOS will likely be overweight or obese (varying degrees) with central (belly) fat with increased percentage of body fat to muscle.

Ideal body fat percentage for adult men age 41-60: 11-22; obese>27%
Ideal body fat percentage adult women age 41-60: 23-35; obese>39%

No known studies have focused on the treatment of dysmetabolic iron overload syndrome and as such, treatment guidelines are not well defined. Physicians may choose to address the individual diseases with medications and use phlebotomy to lower the elevated ferritin. In one study investigators found that patients with DIOS whose ferritin levels were greater than 450ng/mL benefited from phlebotomy (blood donation).

Some patients with dysmetabolic syndrome and only mildly elevated levels of cholesterol, triglycerides or blood pressure, but who have not yet developed diabetes may be able to correct or normalize these levels with a strict diet and exercise program directed at reduction of the percentage of body fat and the improvement of antioxidant capability. There may still be a role for iron redution in such persons.

When the serum ferritin is abnormally high, and TS% is abnormally high, this requires iron reduction with blood donation or phlebotomy.
When the serum ferritin is high but TS% is normal, generally, the cause is due to a fatty liver and inflammation a pattern often seen in people with DIOS.
When the TS% is high but the SF is normal or low, this is called iron avidity.



Visit our websites for more single topic articles:
www.hemochromatosis.org OR www.iron disordisorders.org

DIOS Resources: journal articles and abstracts

Steinberg, K. K. et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. *JAMA*. 285, 2216-2222 (2001).

Mainous, A. G., III, Wells, B. J., Everett, C. J., Gill, J. M. & King, D. E. Association of ferritin and lipids with C-reactive protein. *American Journal of Cardiology*. 93, 559-562 (2004).

Tavill, A. S. & Adams, P. C. A diagnostic approach to hemochromatosis. *Canadian Journal of Gastroenterology*. 20, 535-540 (2006).

Zacharski, L. R., Ornstein, D. L., Woloshin, S. & Schwartz, L. M. Association of age, sex, and race with body iron stores in adults: analysis of NHANES III data. *American Heart Journal*. 140, 98-104 (2000).

Zacharski, L. R. Chow BK, Howes PS, Shamayeva G, Baron JA, Dalman RL, Malenka DJ, Ozaki CK, Lavori PW. Reduction of iron stores and cardiovascular outcomes in patients with peripheral arterial disease: a randomized controlled trial. *JAMA*. 297, 603-610 (2007).

Zacharski, L. R. Chow BK, Howes PS, Shamayeva G, Baron JA, Dalman RL, Malenka DJ, Ozaki CK, Lavori PW. Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial. *Journal of the National Cancer Institute*. 100, 996-1002 (2008).

McLaren, G. D. McLaren CE, Adams PC, Barton JC, Reboussin DM, Gordeuk VR, Acton RT, Harris EL, Speechley MR, Sholinsky P, Dawkins FW, Snively BM, Vogt TM, Eckfeldt JH; Clinical manifestations of hemochromatosis in HFE C282Y homozygotes identified by screening. *Canadian Journal of Gastroenterology*. 22, 923-930 (2008).

Phatak, P. D., Bonkovsky, H. L. & Kowdley, K. V. Hereditary hemochromatosis: time for targeted screening. *Annals of Internal Medicine*. 149, 270-272 (2008).

Weinberg, ED. The hazards of iron loading. *Metallomics*. 2, 732–740 (2010)

Simka M, Rybak Z. Hypothetical molecular mechanisms by which local iron overload facilitates the development of venous leg ulcers and multiple sclerosis lesions. *Medical Hypotheses*. 71(2):293-7 (2008).

Zandman-Goddard G, Shoenfeld Y. Hyperferritinemia in autoimmunity. *The Israel Medical Association Journal*. 10(1):83-4 (2008).

Ristić S, Lovrecić L, Brajenović-Milić B, Starcević-Cizmarević N, Jazbec SS, Sepcić J, Kapović M, Peterlin B. Mutations in the hemochromatosis gene (HFE) and multiple sclerosis.*Neuroscience Letters*. 383(3):301-4 (2005).

Todorich BM, Connor JR. Redox metals in Alzheimer's disease. *Annals of N Y Academy of Science*. 1012:171-8 (2004).

Rubio JP, Bahlo M, Tubridy N, Stankovich J, Burfoot R, Butzkueven H, Chapman C, Johnson L, Marriott M, Mraz G, Tait B, Wilkinson C, Taylor B, Speed TP, Foote SJ, Kilpatrick TJ.Extended haplotype analysis in the HLA complex reveals an increased frequency of the HFE-C282Y mutation in individuals with multiple sclerosis. *Human Genetics*. 114(6):573-80 (2004).

Cutler P.Iron overload and psychiatric illness. *Canadian Journal of Psychiatry*. 39(1):8-11 (1994).

Davies PJ. Was Beethoven's cirrhosis due to hemochromatosis? *Renal Failure*. 17(1):77-86 (1995).

Dieguez S. A man can be destroyed but not defeated': Ernest Hemingway's near-death experience and declining health. *Frontiers of Neurology and Neuroscience*. 27:174-206 (2010).

Chen LY, Chang SD, Sreenivasan GM, Tsang PW, Broady RC, Li CH, Zypchen LN.Dysmetabolic hyperferritinemia is associated with normal transferrin saturation, mild hepatic iron overload, and elevated hepcidin. *Annals of Hematology*. 90(2):139-43 (2011).

Ruivard M, Lainé F, Ganz T, Olbina G, Westerman M, Nemeth E, Rambeau M, Mazur A, Gerbaud L, Tournilhac V, Abergel A, Philippe P, Deugnier Y, Coudray C.Iron absorption in dysmetabolic iron overload syndrome is decreased and correlates with increased plasma hepcidin. *Journal of Hepatology*. 2009 50(6):1219-25.

Fix OK, Kowdley KV.Hereditary hemochromatosis. *Minerva Medica*. 99(6):605-17 (2008).

Riva A, Trombini P, Mariani R, Salvioni A, Coletti S, Bonfadini S, Paolini V, Pozzi M, Facchetti R, Bovo G, Piperno A.Revaluation of clinical and histological criteria for diagnosis of dysmetabolic iron overload syndrome. *World Journal of Gastroenterology*. 4;14(30):4745-52 (2008).

Ruivard M.[Genetic iron overloads and hepatic insulin-resistance iron overload syndrome: an update]. *Review of Medicine Internal*. 30(1):35-42 (2009).

Deugnier Y, Turlin B.Pathology of hepatic iron overload. *World Journal of Gastroenterology*. 21;13(35):4755-60 (2007).

Lainé F, Reymann JM, Morel F, Langouët S, Perrin M, Guillygomarc'h A, Brissot P, Turmel V, Mouchel C, Pape D, Bellissant E, Deugnier Y.Effects of phlebotomy therapy on cytochrome P450 2e1 activity and oxidative stress markers in dysmetabolic iron overload syndrome: a randomized trial. *Alimentary Pharmacology & Therapeutics*. 15;24(8):1207-13 (2006).

Tarantino G, Conca P, Sorrentino P, Ariello M. Metabolic factors involved in the therapeutic response of patients with hepatitis C virus-related chronic hepatitis. *Journal of Gastroenterology & Hepatology*. 21(8):1266-8 (2006).

Vantyghem MC, Girardot C, Boulogne A, Wemeau JL.[Iron overload and insulin resistance]. *Presse Medical Journal*. 5;34(19 Pt 1):1391-8 (2005).

Roblin X, Phelip JM, Hilleret MN, Heluwaert F, Bonaz B, Zarski JP.[Correction of insulin resistance syndrome does not cause normalisation of hyperferritinaemia]. *Gastroenterology & Clinical Biology*. 27(12):1079-83 (2003).

Vénat L, Loustaud-Ratti V, Liozon E, Soria P, Nadalon S, Gissot V, Labrousse F, Vidal E.[Dysmetabolic hepatosiderosis, characteristics in 51 patients]. *Presse Medical Journal*. 8;32(9):400-5 (2003).

Altes A, Remacha AF, Sureda A, Martino R, Briones J, Brunet S, Baiget M, Sierra J.Patients with biochemical iron overload: causes and characteristics of a cohort of 150 cases. *Annals of Hematology*. 82(2):127-30 (2003).

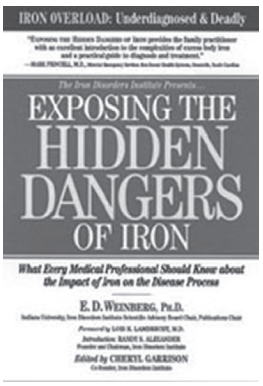
Piperno A. Classification and diagnosis of iron overload. *Haematologica*. 83(5):447-55 (1998).

Read Cheryl's story: a case of mild DIOS managed with diet and exercise program.

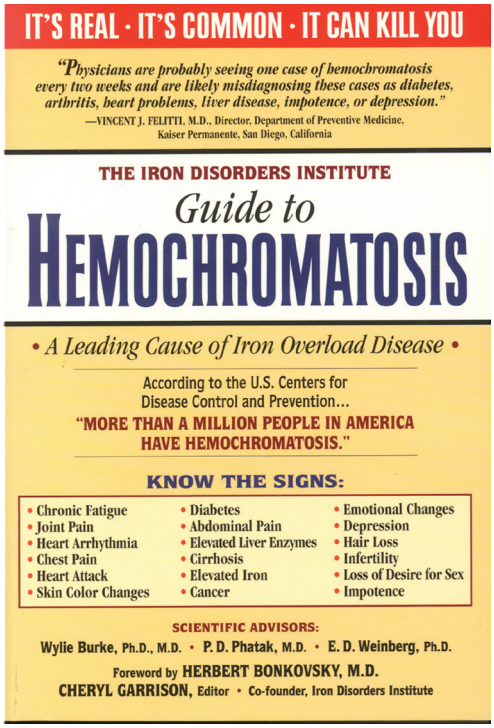
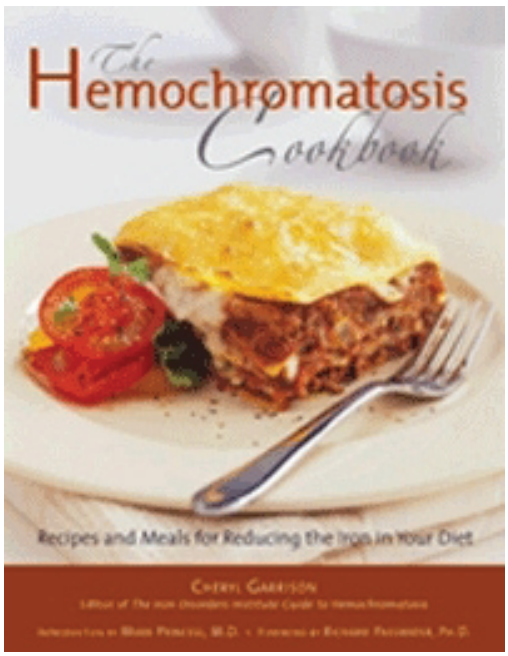
Excerpts from Cheryl's Story:

Cheryl Garrison, co-founder and Executive Director of Iron Disorders Institute (IDI) was told by her physician in 2008 that she had hemochromatosis. Her doctor was basing the diagnosis on an elevated serum ferritin. Cheryl's blood pressure and lipids were elevated; she had a fatty liver and serious gall bladder issues. After re-reading the books about iron published by IDI she realized that her condition was more in line with dysmetabolic syndrome (DIOS). "I remember Dr. Herbert Bonkovsky telling us in 2000 that fatty liver disease was going to be the next big health issue." recalls Cheryl. Blood pressure and lipid lowering medications were not well tolerated. "I had no choice but to try diet and exercise. After a few weeks on a particular approach, I began to see the first improvements in fat reduction. I am still working on blood pressure." she remarks. Cheryl is willing to share with you what she did, but points out that her approach is not stated as policy for Iron Disorders Isntitute (IDI).

Contact Cheryl for a copy of her experience:
cgarrison@irondisorders.org



For medfical professionals: Dr. Gene Weinburg's book describes body systems and how too much iron impedes normal function and results in disease.

Order online
www.irondisorders.org
www.hemochromatosis.org
or through any major bookstore!

Books for the Patient