

Hemochromatosis Update

By Vincent J Felitti, MD

Introduction

If a person must have a genetic disease, hemochromatosis is the one to have. Although its mutation is the most common potentially fatal mutation in North America, hemochromatosis can be diagnosed early, treated simply and effectively, and can even be prevented. Hemochromatosis has also recently been selected by the National Institutes of Health as a model for helping physicians learn about treating genetic disease.

As an update to a 1999 clinical article on hemochromatosis that appeared in *The Permanente Journal*,¹ the present article presents information from a recent study of 41,038 Kaiser Permanente (KP) members in San Diego, each of whom had comprehensive biopsychosocial evaluation, genetic analysis for the HFE (hemochromatosis) gene, and measurement of iron load; this testing allowed genotype to be matched against iron load and physical findings. For the first time, a large control group was included to determine the extent to which the symptoms compatible with iron overload were actually caused by—not merely coincident with—iron overload. The purpose of the present article is to help physicians integrate this new clinical information into daily practice throughout the Kaiser Permanente Medical Care Program.

Clarifying the Nomenclature

The nomenclature for hemochromatosis presents a serious problem

that has implications for all genetic disease. For example, the term hemochromatosis is currently applied to several different conditions (some of which are nongenetic):

- mutation of the HFE gene regardless of activity or penetrance of the mutation;
- states of iron overload ranging from trivial to severe regardless of genotype;
- clinical cases of iron overload disease regardless of genotype; and
- iron overload disease caused specifically by the HFE mutation.

A moment's reflection indicates the potential for confusion for patients as well as for physicians. This article cannot resolve permanently the confusion caused by such careless use of nomenclature; instead, to describe the logical progression of iron overload, I use the following nomenclature:

- homozygous mutation of the HFE gene;
- increased iron absorption (iron loading);
- iron overload states;
- clinical iron overload disease, or hemochromatosis (regardless of genotype); and
- hereditary hemochromatosis.

This nomenclature may be somewhat awkward, but precisely distinguishing these different states is the only way to prevent confusion about this increasingly recognized disorder and to promote better understanding of it. Moreover, the main principle established here is applicable to all other genetic dis-

eases: Presence of a genetic mutation must not be equated with existence of a genetic disease. The term *hemochromatosis* should be reserved for the disease state (organ damage), not for mutations or preclinical states.

Pathophysiology of Hemochromatosis

Although iron is essential for life, substantially excessive levels of iron are toxic. The essence of iron overload *disease* (ie, hemochromatosis and genetic hemochromatosis) is the iron load, not the mutation.

In normal circumstances, iron absorption is constant despite variation in dietary iron levels because the HFE gene on chromosome six limits intestinal iron absorption to about 1.5 mg/day. When mutations damage certain portions of the HFE gene, increased iron absorption may (but does not necessarily) occur. If increased iron absorption does occur, the total body iron load may, given enough time, build to toxic levels because no existing biologic mechanism facilitates excretion of excess iron. Given enough time, slowly incremental additions to iron load can—like compound interest—produce major effects that depend on the rate of iron accumulation. This time factor is important to remember because it has major clinical implications.

The wide range of organ damage that potentially ensues from clinically significant iron overload is

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termed *clinical hemochromatosis* or *iron overload disease*. Although hemochromatosis is often remembered as “bronze diabetes with cirrhosis,” the range of clinical presentations is vastly greater, as previously described in a 1999 article in *The Permanente Journal*.¹ Just as congestive heart failure is not the same as hypertensive cardiomegaly, hemochromatosis is not the mutation and not subclinical iron overload; it is iron overload *disease*. The genetic (and most common) form of hemochromatosis is thus properly termed hereditary hemochromatosis, whereas nongenetic forms of iron overload disease are properly termed hemochromatosis.

The HFE gene can be damaged by several mutations (polymorphisms) occurring at different loci within the gene. One of these mutations is recognized as the “major” mutation because it is the one most commonly found in patients with severe clinical iron overload. The major mutation of the HFE gene is described either as occurring at the 845-nucleotide locus or as the C282Y mutation, depending on the notation system used. Patients are also commonly tested for presence of the 187-nucleotide or H63D mutation, which is much less likely to be associated with clinically significant iron overload. Other relevant mutations may exist undiscovered within the HFE gene, and other genes that affect iron absorption may exist undiscovered. The single heterozygous state (carrier) of either of these mutations has no currently known clinical consequence. Heterozygotes are currently believed to function as genetically normal, because they are not asso-

ciated with iron overload; more than 30 million Americans are heterozygous (carriers) for the major HFE mutation. In the unlikely event that this population does have iron overload, it will not be attributable to the carrier state of affected persons. By contrast, clinically significant iron overload develops in about one of every 50 people who are carriers of *both* mutations (ie, compound heterozygotes—one copy of each of the two common mutations).

Kaiser Permanente (KP) in San Diego was the first institutional setting in the nation to routinely perform once-in-a-lifetime screening for iron overload. Because of both our uniquely high volume of iron screening and our comprehensive program of biopsychosocial evaluation, Dr Ernest Beutler at Scripps Research Institution proposed a collaborative study of hemochromatosis to learn more about its clinical manifestation, diagnosis, and treatment. Results of this study^{2,3} have led to important changes in our understanding of iron loading and hemochromatosis.

This study was the first large, population-based, controlled study done to determine the symptom prevalence of potentially iron-related findings and iron loads in patients with and without the homozygous major mutation. This aspect of the study is of singular importance because the signs or symptoms of hemochromatosis are compatible with—but not specific for—iron overload disease, and many of these symptoms are prevalent to a substantial extent in the general population. For instance, diabetes and arthritis are common in middle-aged and older adults and can result from

iron overload disease, but how often are these conditions actually caused by it? In which patients are these conditions part of the population background prevalence; in which patients are they attributable to the homozygous HFE mutation? We were surprised to discover that our study was the first to address this problem in a large sample.

The present article describes our study findings and discusses their relevance to daily clinical practice.

Study Design

The study population consisted of 41,000 consecutive, consenting adults undergoing comprehensive medical evaluation in the Health Appraisal Center at the KP San Diego Department of Preventive Medicine. We tested each of these 41,000 study subjects for serum iron saturation, serum ferritin level, and known HFE mutations. All participants had detailed biomedical, psychologic, and social evaluation. We recorded all signs and symptoms potentially attributable to iron overload.

Prevalence of the homozygous major mutation—approximately five cases per thousand study subjects—was confirmed within the HFE gene, but we also found that this mutation was activated in only about half the mutated subjects. For example, two of my patients are elderly sisters who live across the street from each other and apparently lead identical lives. Both sisters are homozygous for the C282Y mutation of the HFE gene and thus have the two copies of the major mutation necessary for hemochromatosis to manifest. However, whereas one sister has clinically significant iron overload that has required lifetime phlebotomy, the other sister has never had phlebotomy, has never been a blood donor, and verges on having iron deficiency. We do not

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yet understand why the major mutation of the HFE gene shows this difference in activity.

In the half of C282Y homozygotes who absorb iron excessively, the amount of iron absorbed is highly variable (in addition to being age-dependent, as noted earlier in this article). This fact raises two basic questions that have broad implications for our evolving understanding of all genetic disease:

- Does the clinical manifestation of hemochromatosis depend on presence of the mutation? Or on iron overload?
- If clinical manifestation of hemochromatosis depends on iron overload, what level of iron overload induces this clinical condition?

We resolved these questions by matching iron load against

- presence of the homozygous major mutation,
- fasting serum iron saturation level,
- serum ferritin level, and
- signs and symptoms compatible with, but not specific for, iron overload disease.

Total body iron load was measured inferentially by serum ferritin level and directly by quantitative phlebotomy. Neither serum iron level nor serum iron saturation was used to measure total body iron load because these—in contrast to serum ferritin level and quantitative phlebotomy—are not valid measures of total body iron load. Serum iron saturation is a measure of iron in transit and of how much that iron saturates its carrier serum proteins, known collectively as transferrin.

Results and Discussion

In this study—possibly the largest genetic analysis study ever carried out in a well-evaluated population—we found that clinical iron over-

load disease—hemochromatosis—is totally a function of iron overload and not a function of the genetic mutation. In addition, we found that unexpectedly high body iron loads are required for organ damage. From analysis of 152 study subjects who were homozygous for the major mutation, we concluded that organ damage begins when serum ferritin level reaches about 1000 ng/mL (1000 mg/L). Given that 81% of all adult Health Plan members pass through the Department of Preventive Medicine at least once in any four-year period, we believe that selection bias did not affect our conclusions.

However, answering the simple question, “What does a physician do with a patient who has a serum ferritin level of 650 ng/mL (650 mg/L)?” is complicated by three factors, the first of which is age. A young patient with ferritin level of 650 ng/mL (650 mg/mL) will probably have a significantly higher ferritin level later in life, given sufficient time. The second complicating factor is that hyperferritinemia can be caused by disorders other than iron overload (eg, alcoholism, chronic hepatitis, malignancy). The third complicating factor is the difficulty of balancing low risk of clinically evident hemochromatosis developing in a patient with a given ferritin level (650 ng/mL, in our example) against the even lower risk presented to this patient by phlebotomy. This article explains why clinicians within the Kaiser Permanente Medical Care Program can answer this third question differently than do clinicians elsewhere.

We addressed these questions carefully for our 41,000 comprehensively evaluated patients and subsequently found that many (but not all) of the symptoms previously attributed either to the mutation or to iron overload had a more mundane

explanation: They were part of the normal prevalence found in the age- and sex-matched control group. Indeed, homozygous penetrance of the major HFE mutation (manifested as clinically significant iron overload) was lower than we expected and was even lower in terms of clinically evident

hemochromatosis. The mutation per se was irrelevant if it did not produce clinically significant levels of iron overload. For example, many diabetic patients who are homozygous for the major HFE mutation are diabetic because of obesity and not because of iron overload: In these patients, the mutation is coincident, not causal.

Patients in our study were distributed along the following spectrum (Figure 1):

- homozygous mutation without activation of the gene (these patients had normal serum iron saturation and normal serum ferritin levels);
- homozygous mutation with increased serum iron saturation but without meaningful iron overload (these patients had normal or minimally elevated serum ferritin level);
- homozygous mutation with increased serum iron saturation and potentially dangerous iron overload;
- homozygous mutation with iron overload and subclinical tissue damage;
- homozygous mutation with iron overload and overt organ damage.

Diagnostic Screening

At present, knowledgeable physicians disagree about whether to screen populations for hemochromatosis.

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KP San Diego became the first institutional setting in the world to follow this practice and has screened more than 350,000 adult Health Plan members in the past eight years. (Ideally, children would be screened instead of adults.) An argument for

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population screening for hemochromatosis is that symptoms do not provide a practical basis for diagnosing hemochromatosis: Symptoms occur late in persons with iron overload; potential symptoms are numerous, nonspecific, and often result

from causes other than hemochromatosis. Using our approach, the benefit of screening has distinctly outweighed the cost; however, such might not be the case elsewhere if screening were done as a stand-alone test or if genetic analysis were used for screening.

In considering genetic disease, clinicians must remember the basic

concept that genotype does not equate with phenotype. In particular, our goal as clinicians working with adult patients is to determine whether they have clinically significant iron overload, not the genetic mutation. Therefore, all Health Plan members seen at the KP San Diego Department of Preventive Medicine are tested once in their lifetime for serum iron saturation. If the fasting iron saturation of the specimen is >50%, the test is repeated and the serum ferritin level is measured. This repeat procedure should be done on an early-morning fasting specimen because of diurnal variation: Higher iron saturations sometimes occur in the morning.

Treatment

Patients who have both persistently elevated iron saturation and hyperferritinemia are entered into the hemochromatosis registry and are seen for consultation by a physician who has experience treating

patients with hemochromatosis. Most of these patients then go to the Donor Center weekly for phlebotomy, during which 500 mL of whole blood is removed until the plasma ferritin level is reduced to approximately 20 ng/mL (20 mg/L). This process is termed *quantitative phlebotomy* because its frequency of application allows blood to be removed faster than iron can be reabsorbed and thus allows accurate calculation of total body iron stores. If more than 12 to 16 phlebotomy procedures are needed to attain this endpoint, the patient is identified as iron-laden and enters the Maintenance Program, a lifetime program in which most patients have 500 mL of whole blood removed by phlebotomy every two months (for men) or every three months (for women). To avoid inducing more than minor anemia, a lower limit is set for the prephlebotomy hematocrit level. Liver biopsy is never performed; it is unnecessary, is not dependable for early diagnosis, has some risk, is costly, and frightens some patients away from completing prescribed diagnostic studies. Genetic analysis is done for many of our suspect cases, because this analysis sometimes clarifies confusing situations and identifies index cases that trigger family screening.

In some circles, much is made of dietary limitations on ingested iron; under normal conditions, however, variations in dietary iron play a minor role that is easily corrected by adjusting the phlebotomy protocol. Nonetheless, some patients choose to strictly limit their dietary intake of iron, perhaps to gain a sense of participatory control of the situation—and this choice is certainly not harmful. Raw shellfish should be avoided because of its occasional contamination with *Vibrio*, an organism that flourishes in high-iron



Figure 1: Illustration shows spectrum of conditions distributed among 41,038 KP members in San Diego who had genetic analysis for the HFE (hemochromatosis) gene and measurement of iron load. (TS= transfusion saturation.)

environments and damaged livers. Alcohol should be avoided or consumed sparingly because of its potential for additive hepatotoxicity; patients should be immunized against hepatitis A and B to prevent this additional possible source of liver damage. Iron supplements should be avoided.

The commonly used term, “iron-rich blood” is misleading because blood from a person affected with hemochromatosis has no more iron than has blood from unaffected persons; blood happens to be the only removable iron-rich tissue that can be readily regenerated. The process of regeneration draws iron from potentially damaging tissue stores in organs elsewhere in the body. This process is why phlebotomy is effective treatment for hemochromatosis.

Hyperferritinemic patients with normal fasting iron saturation are evaluated for causes of hyperferritinemia other than iron overload—most commonly, unrecognized alcoholism or chronic hepatitis. And because iron overload, alcoholism, and chronic hepatitis are relatively common conditions, they coexist in some patients. Quantitative phlebotomy readily identifies the portion of hyperferritinemia attributable to iron overload.

The therapeutic benefit of normalizing iron levels in iron-laden patients is obvious: Hemochromatosis can be prevented in these patients when they are identified and treated presymptomatically. Moreover, the transfusable blood generated by treatment creates a valuable byproduct. In 2001, 40% of the blood transfused at KP San Diego was obtained from the hemochromatosis phlebotomy program. If purchased from the Red Cross, this blood would have a market value in excess of \$300,000. In addition, we have coincidentally identified a

number of cases of previously unrecognized chronic hepatitis and alcoholic liver damage.

To make this areawide screening successful, we have had to solve several problems: physician unfamiliarity with iron overload, lack of time for patient education, and the difficulty and complexity of tracking treatment for a large population. The problem of physician unfamiliarity with iron overload was initially solved by centralized screening and follow-up, and this article takes a further step toward decentralizing treatment and follow-up of iron-laden patients. The next problem was that providing patients with adequate information about this (or any) genetic disease is time-consuming and unreliable when done during a traditional office visit (however lengthy), whether to a physician or to a genetics counselor. We resolved this problem by developing a videotape⁴ with accompanying booklet⁵ that we mail to patients before they arrive for their consultation. We solved the third problem by creating a computerized hemochromatosis registry that allows us to efficiently follow treatment progress over time and to maximize follow-up. This solution was enhanced by coordination with the KP San Diego Blood Donor Center, created earlier by Michael Bonin, MD, Chief of Pathology. This important resource has been invaluable for simplifying the process of phlebotomy and has substantially added to our blood supply available for transfusion. By contrast, phlebotomy in the community is needlessly time-consuming, remarkably expensive, and often difficult to arrange.

Physicians whose practice includes treatment of hemochromatosis ultimately are likely to attract some patients with somatization dis-

orders who desperately hope they have hemochromatosis so that their medical condition can finally be diagnosed and treated effectively. Chronic fatigue, arthralgia, and depression can be caused by iron overload; however, in most patients with iron overload, these symptoms are not caused by the iron overload. Understandably, nonetheless, many patients who have heard of hemochromatosis attribute their symptoms to this condition. This problem is further aggravated when persons with an inactive HFE mutation or minimal hyperferritinemia are incorrectly told that they have hemochromatosis. Attempting to correct this misinformation is a major task that easily triggers patient mistrust and anger. This problem reflects our general ineffectiveness at dealing with these psychosomatic symptoms; the solution lies in the difficult feat of learning to effectively treat somatization disorders.

At KP San Diego, we tell homozygotes who have no active iron loading process that they are normal; we do not explain the technical details behind our conclusion because they are needlessly confusing to patients. In contrast, anyone who is significantly iron-laden for any reason enters the phlebotomy program. When an index case is identified—whether by iron overload or by homozygosity—we give the index patient multiple copies of a Letter for Relatives that urges primary relatives to be screened. Only about one third of these relatives follow this advice.

Summary

From our experience screening more than 350,000 adult Health Plan members for iron overload, I firmly believe in the value of once-

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per-lifetime screening for everyone. Improperly done, the test is unaffordable; but properly done, the test costs about the same as a complete blood count (CBC). Because people are damaged by the iron overload and not by the genetic mutation, screening is done by chemical test, not by genetic analysis. Moreover, as we described in *Lancet*,² half the homozygotes never begin any iron loading. Of the half that do begin iron loading, most do so to an inconsequential extent. Problematic levels of iron overload develop in only a small percentage of the homozygotes. Organ damage starts when plasma ferritin levels reach approximately 1000 ng/mL (1000 mg/L). A 70-year-old person with plasma ferritin level of 350 ng/mL

(350 mg/L) will never be adversely affected by iron overload, but the same plasma ferritin level in a 20-year-old person can have unpredictable consequences.

This problem of whom to treat for iron overload is similar to that seen with hypertensive patients: Not every hypertensive patient eventually has a stroke, congestive heart failure, or renal failure; we safely treat the many to help the few. One difference between the two conditions, however, is that antihypertensive medications are often expensive and sometimes have side effects, whereas phlebotomy is overwhelmingly well tolerated. If we are uncertain about whom to treat, we should err on the side of safety and, by conducting quantitative phlebotomy to determine actual iron load, then decide any maintenance strategy on the basis of that iron load. ❖

References

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Don't Give Up

Hope begins in the dark, the stubborn hope that if you just show up and try to do the right thing, the dawn will come. You wait and watch and work: You don't give up.

— Anne Lamott, b 1954, author