REVIEW ARTICLE

Plasma ferritin concentrations: their clinical significance and relevance to patient care

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In healthy persons the plasma ferritin concentration is a sensitive index of the size of body iron stores. It has been successfully applied to large-scale surveys of the iron status of populations. It has also proved useful in the assessment of clinical disorders of iron metabolism. A low plasma ferritin level has a high predictive value for the diagnosis of uncomplicated iron deficiency anemia. It is of less value, however, in anemia associated with infection, chronic inflammatory disorders, liver disease and malignant hematologic diseases, for which a low level indicates iron deficiency and a high level excludes it, but intermediate levels are not diagnostic. Measuring the plasma ferritin concentration is also useful for the detection of excess body iron, particularly in idiopathic hemochromatosis, but again it lacks specificity in the presence of active hepatocellular disease. If iron overload is suspected in these circumstances determination of the iron content of a percutaneous liver biopsy specimen is required. In families with idiopathic hemochromatosis the combined determination of the plasma ferritin concentration and the transferrin saturation is a sufficient screen to identify affected relatives; however, estimation of the hepatic iron concentration is required to establish the diagnosis.

Chez les personnes saines la concentration en ferritine plasmatique est un index sensible de l'importance des réserves corporelles de fer. Elle a été appliquée avec succès à des enquêtes à grande échelle sur les réserves de fer de diverses populations. Il s'est également montré utile pour l'évaluation des troubles cliniques du métabolisme du fer. Un faible taux de ferritine plasmatique possède une valeur prévisionnelle élevée pour le diagnostic d'une anémie ferriprive sans complication. Il est de moindre valeur, toutefois, lors d'anémies reliées à une infection, à un trouble inflammatoire chronique, à une maladie hépatique ou à des maladies hématologiques malignes, pour lesquels un taux faible indique une carence en fer et un taux élevé l'exclut, mais des taux intermédiaires n'ont pas de valeur diagnostique. La mesure de la concentration de la ferritine plasmatique est aussi utile pour détecter un excès de fer du corps, particulièrement dans l'hémochromatose idiopathique, mais là encore elle manque de spécificité en présence d'une maladie hépatocellulaire active. Si une surcharge en fer est soupçonnée dans ces circonstances la détermination de la teneur en fer d'une pièce de biopsie hépatique transcutanée est nécessaire. Dans les familles atteintes d'hémochromatose idiopathique la détermination combinée de la concentration en ferritine plasmatique et de la saturation de la transferrine est un test de dépistage suffisant pour identifier les parents affectés; toutefois, il faut estimer la concentration de fer hépatique afin d'établir le diagnostic.

The healthy adult human has a total body iron content of about 3500 mg, of which 2000 mg is present as circulating hemoglobin, 300 mg is in the form of cell enzymes and pigments, and the remainder is stored in cells as ferritin or hemosiderin. Ferritin is a macromolecule composed of a protein shell within which up to 4500 atoms of iron can be stored as ferric oxyhydroxide.[1] Hemosiderin is probably a degraded form of ferritin that has lost part of its protein shell.

Iron is stored mainly in the reticuloendothelial cells of the bone marrow, liver and spleen and in the parenchymal cells of the liver, which accept any excess of iron in the body. When iron in these sites is needed by other tissues the stores release it into the blood, where transferrin carries it to the appropriate tissue; once the need has been met the stores are reconstituted.

Most of the iron in the blood is destined for the erythropoietic marrow, where it is incorporated into

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hemoglobin. Circulating erythrocytes are normally destroyed at the end of their life span by the reticuloendothelial cells in the spleen and liver. Most of the iron from degraded hemoglobin returns to the plasma, but a small part first exchanges slowly with the iron stores in the reticuloendothelial cells, then either returns to the bone marrow to be incorporated into hemoglobin or enters iron storage sites, where it exchanges with tissue ferritin.

Although ferritin is predominantly an intracellular protein, minute amounts circulate in the plasma.[2] The availability of sensitive radioimmunoassays for plasma ferritin has stimulated a great deal of interest in the use of plasma ferritin concentrations to evaluate disorders of iron metabolism.[3-12] A salient result of this research has been the discovery that the plasma ferritin concentration in healthy persons is directly proportional to the size of the body iron stores: 1 ng/ml of plasma ferritin corresponds to approximately 5 to 9 mg of storage iron.[13-15] This finding has had clinical application in nutrition surveys and in the diagnosis of iron deficiency and iron overload. The renewed clinical interest in ferritin has also led to the investigation of the microheterogeneity of the protein in the tissues, but I will not cover this in my review because it does not yet have clinical application.[16]

Identical ferritin values have been obtained in serum and plasma from blood treated with ethylenediamine tetra-acetic acid or heparin;[3] for the sake of consistency I have referred to plasma ferritin throughout this paper.

Plasma ferritin concentration

Healthy persons

During infancy, childhood and early adolescence the median plasma ferritin concentration progressively increases from 10 to 45 ng/ml in both boys and girls.[17-19] During adolescence the levels diverge. With the male adolescent growth spurt the median level rises sharply to a plateau of approximately 90 ng/ml and remains there during adulthood; in the female, however, the level stays between 25 and 30 ng/ml during the reproductive period because of menstruation, with its attendant loss of iron, and pregnancy, with its depletion of body iron stores. When the iron requirements of women diminish following the menopause the median plasma ferritin concentration gradually rises.[18,19]

Although the changes in the median plasma ferritin concentration correspond to known changes in the size of the body iron stores, there is marked individual variation. In a random survey of 697 Canadians aged 20 years or over the 5th and 95th percentiles of the plasma ferritin concentration were found to be, respectively, 20 and 450 ng/ml in men and 5 and 200 ng/ml in women.[18] Among persons without anemia or iron deficient erythropoiesis the geometric mean plasma ferritin concentration in 152 women was 34 ng/ml (95% confidence interval 9 to 125 ng/ml) and the mean in 174 men was 95 ng/ml (95% confidence interval 27 to 329 ng/ml).[19]

Pregnant women and newborn and older healthy infants

To meet the iron requirements of the fetus the mother must mobilize an additional 250 to 300 mg of iron, particularly during the last 6 months of pregnancy. Measurements of the plasma ferritin concentration have been helpful in monitoring the impact of pregnancy on iron metabolism. The pronounced fall in the average plasma ferritin concentration to low levels in late pregnancy indicates that maternal iron stores are utilized to meet fetal requirements.[20,21] Unless iron supplements are provided during pregnancy maternal iron depletion often develops.[20] Nevertheless, the plasma ferritin levels in the newborn are comparatively high and do not correlate with the plasma ferritin levels of the mother.[20,22] After delivery the hemoglobin concentration of the mother returns to normal within 3 months but the mean plasma ferritin concentration remains very low.[20] Iron supplements are required for at least 3 months after delivery to replenish iron stores. The plasma ferritin assay is a useful method of identifying pregnant women with depleted iron stores who require iron therapy and subsequently assessing their response to treatment.

The changes in the average plasma ferritin levels of groups of infants during the first year of life correlate well with the changes in size of the body iron stores during infancy.[23] The average plasma ferritin concentration of infants rises sharply during the first month of life, when iron shifts from the erythrocyte to the storage compartment.[17,23] It then falls over the next 3 months as iron is used or deployed to meet the needs of a rapidly expanding erythrocyte mass.[22]

Relation to reticuloendothelial iron content

There is good agreement between the plasma ferritin concentration and both the semiquantitative visual assessment of the amount of stainable iron in bone marrow smears and the quantitative measurement of the amount of ferritin in bone marrow aspirates in persons with iron stores that vary widely.[24-28] Alterations in the reticuloendothelial iron content are followed by changes in the plasma ferritin concentration. As iron stores are lowered by repeated venesection the plasma ferritin concentration falls, but it rises when the iron stores are replenished with iron given orally or parenterally.[14,29,30] In patients with pernicious anemia high plasma ferritin levels fall after vitamin B_{12} therapy as iron stores are mobilized for erythropoiesis.[31] Conversely, a single episode of fever, which restricts the release of iron from senescent erythrocytes by the reticuloendothelial cells, leads to a stimulation of ferritin production and an increase in the plasma ferritin level.[32] Thus, the reticuloendothelial iron stores are an important factor governing the plasma ferritin level, and their size can be gauged from it.

Correlation with other parameters of iron metabolism

In ostensibly healthy persons a weak inverse relation was observed between the plasma ferritin concentration and the total iron binding capacity but not the serum iron concentration, the transferrin saturation or the erythrocyte protoporphyrin content.[19] The results of iron ab-

sorptive measurements made by whole body counting of radioactivity have revealed a linear and highly significant relation between the absorption of radioactive iron and the log plasma ferritin concentration:[14,25,26,28,33,34] the iron absorption progressively falls as the plasma ferritin concentration increases. Moreover, a positive correlation has been found between plasma and duodenal ferritin concentrations in healthy persons and patients with iron deficiency or iron overload.[35] The possibility that iron absorption may be regulated by the plasma ferritin concentration has been tested in rats: the intravenous infusion of ferritin prepared from rat liver had no effect on iron absorption despite a 100-fold difference in the circulating ferritin concentration.[38] Whether plasma ferritin is also ineffective in this regard remains to be determined.

Biochemical characteristics of ferritin

Although plasma ferritin levels are normally closely related to the amount of tissue ferritin, there are several distinct biochemical differences between the two types of ferritin:

- Plasma ferritin has a lower affinity than tissue ferritin for an anion exchange column, presumably because of differences in the structure of the molecules.[37]
- Plasma ferritin, in contrast to tissue ferritin, remains near the top of a sucrose density gradient during centrifugation, and it has a low iron content.[38]
- The pattern of plasma ferritin on isoelectric focusing is similar to that of natural apoferritin.[38]
- A high proportion of plasma ferritin, unlike tissue ferritin, binds to concanavalin A, which suggests that the protein contains carbohydrate moieties.[39,40]

While it is evident that plasma ferritin resembles apoferritin it is not known whether plasma ferritin is synthesized with a low iron content in the tissues or loses its iron as it enters the plasma. The molecule appears to be modified by the addition of carbohydrate residues during secretion or release from the tissues.

Metabolism of ferritin

At least part of the iron in plasma ferritin originates in the reticuloendothelial system from the degradation of senescent erythrocytes. In rats plasma ferritin was found to be labelled after the intravenous administration of heat-damaged erythrocytes labelled with iron 59 but not after the injection of ^{59}Fe-transferrin or ^{59}Fe-hemoglobin–heptoglobin, or after the oral administration of ^{59}Fe-citrate.[41]

The metabolic destination of plasma ferritin is unknown. In one study ferritin purified from rat liver, labelled with radioactive iron and given intravenously disappeared from the plasma of rats at an exponential rate, with an average half-life of 4 minutes.[41] Within 1 hour most of the radioactive iron had accumulated in the liver. The plasma clearance of recrystallized hepatic or splenic ferritin in the dog was also found to be rapid and not limited by the plasma concentration.[42] The iron and protein moieties were removed simultaneously, but clearance of the protein was slower when the iron was removed by thioglycollate treatment before intravenous injection. The plasma half-life of iron-poor ferritin prepared by ultracentrifugation from liver ferritin was found to be identical to that of liver ferritin in the rat,[40] but the presence of carbohydrate in ferritins of different tissue origin delayed their disappearance from the plasma.[40]

Plasma ferritin may play an important role in iron kinetics; however, these studies were carried out with ferritin prepared from tissues. Whether plasma ferritin behaves in a similar manner remains to be established. No direct measurements of plasma turnover in humans have been reported, but serial measurements of the plasma ferritin concentration in neonates undergoing exchange transfusion have suggested that plasma ferritin turnover is also very rapid.[43] The clinical significance of these observations is not clear.

Uses of plasma ferritin concentration

Population surveys of iron deficiency

In otherwise healthy persons the plasma ferritin concentration is a sensitive index of the earliest stage of iron deficiency — depletion of the body iron reserves. A low transferrin saturation or a high erythrocyte protoporphyrin content is helpful in identifying an intermediate stage in which there is an inadequate iron supply for erythropoiesis. The hemoglobin concentration is an index of the severity of the deficiency.

No single test of the iron status of a population is without its pitfalls. Interpretation of all measurements is complicated by the fact that conditions such as chronic infection, chronic inflammation and liver disease may produce a shift in iron from erythrocytes to reticuloendothelial cells, with an increase in the plasma ferritin concentration, a reduction in the transferrin saturation and a fall in the hemoglobin concentration.

To enhance specificity the use of two or more tests has been advocated, and an arbitrary decision has been made to call iron-deficient those individuals showing abnormal results in two or more tests. Cook, Finch and Smith[19] and Derman and colleagues[44] reported that the combination of a low serum ferritin concentration and a low transferrin saturation was a better predictor of iron deficiency anemia in population surveys than either finding alone. While the use of two or more tests increases the proportion of true-negative results (specificity) it decreases the proportion of true-positive results (sensitivity).[45] For example, when both the transferrin saturation and the serum ferritin concentration were used as diagnostic indices in a Canadian nutrition survey the overall prevalence of iron deficiency was found to be half of that derived previously from the serum ferritin concentration alone.[46]

Plasma ferritin analysis was used in large-scale surveys of the iron status of populations of the United States, South Africa and Canada.[18,19,44] The plasma ferritin data in the North American surveys indicated that, while the values in men appeared to be the standard of "normality", iron deficiency characterized by a low plasma ferritin concentration was prevalent in children,

adolescents and menstruating women. However, a reduction in iron reserves great enough to impair erythropoiesis was found in only 2% to 3% of the survey participants. The results of a survey of Canadians resident in the 10 provinces (excluding Indians in bands and persons in institutions and military camps) indicated that the dietary iron intake was sufficient to meet the needs of erythropoiesis but insufficient to establish appreciable iron reserves in about one third of the children, adolescents and young women. The prevalence of low iron stores in the provincial residents and in the Indians was similar.[46] In contrast, the prevalence of iron deficiency was lower in Inuit in the Territories than in either of the other two groups. Obviously, the diets of many infants, children, adolescents and women of reproductive age in North America require more iron-rich foods for the development of body iron reserves.

Assessing the iron stores of blood donors

Insufficient attention has been given to the iron status of blood donors. The frequency of blood donation has been so adjusted as to prevent anemia in most donors, but little attention has been paid to the effect of phlebotomy on the reduction of the total body iron content. Recently Finch and coworkers[47] found that one donation per month halved the plasma ferritin level in men and that more frequent donation was associated with further decreases. Men were able to donate two to three units per year without appreciable iron deficiency, as defined by a plasma ferritin value of less than 12 ng/ml. Women could donate only about half this amount, and giving blood more often was associated with a high frequency of depleted iron stores and donor dropout. Birgegård and associates[48] also found that blood donations at a mean interval of 10 weeks reduced the plasma ferritin level in men and that there was a high risk of iron deficiency after about six donations. The risk was far less if more than 1000 mg of iron was taken orally between donations.

Plasma ferritin assays are a method of determining the suitability of persons for giving blood without exhausting their body iron reserves. The time, however, between drawing blood and obtaining the plasma ferritin level with current assays presents an obstacle to their use.

Diagnosing and monitoring the treatment of iron deficiency anemia

The plasma ferritin concentration is reduced in uncomplicated iron deficiency.[24,25,29,49-51] Its measurement in mild iron deficiency anemia has considerable advantage over measurement of the serum iron concentration and the transferrin saturation, which are often within normal limits at this stage. When iron deficiency anemia is associated with chronic infection, rheumatoid arthritis, widespread cancer, malignant hematologic disorders or liver disease, neither the plasma ferritin concentration nor the transferrin saturation is a valid index of iron deficiency.[24,51-57]

A study of the usefulness of measuring the plasma ferritin concentration to detect iron deficiency in a general hospital showed that the predictive value of a low result for the presence of iron deficiency was 39% for the transferrin saturation and 83% for the plasma ferritin concentration, whereas the predictive value of a normal or a high result for excluding iron deficiency was 93% or 94% respectively.[56] The plasma ferritin concentration and the transferrin saturation were equally sensitive as indicators of iron deficiency, but the former was more specific.

In an anemic patient a plasma ferritin concentration of less than 12 to 18 ng/ml, depending on the method of analysis, indicates iron deficiency, and a concentration greater than 100 ng/ml excludes it. When the value is intermediate histologic determination of the grade of bone marrow hemosiderin is the most reliable test for iron deficiency anemia. Measuring the plasma ferritin concentration has also helped to differentiate the hypochromic microcytic anemia of β-thalassemia trait from iron deficiency anemia.[58] No condition except iron deficiency has been reported to produce a low serum ferritin concentration.

Plasma ferritin assays have been used to measure the accumulation of storage iron in patients treated for iron deficiency anemia.[59,60] The results have shown that oral iron treatment needs to be continued for 2 months to replenish iron stores after the hemoglobin concentration has reached normal values.[59] This is long enough if the cause of the iron deficiency has been corrected.

Patients with malignant hematologic diseases

Normal peripheral blood leukocytes contain ferritin; its concentration is higher in monocytes than in lymphocytes or neutrophils.[61,62] It is not surprising that high plasma ferritin concentrations have been observed in patients with leukemia, the highest levels having been in those with acute myeloblastic leukemia.[63] The plasma ferritin in these patients is derived from the leukemic cells.[63] Plasma ferritin concentrations returned to normal after the successful treatment of acute lymphatic leukemia, but this has not yet been shown to be of value in clinical management.[64]

A high plasma ferritin level has been found in patients with Hodgkin's disease, particularly when the disease is advanced.[65] It is often associated with a low transferrin saturation and appears to result at least in part from a nonspecific response of the reticuloendothelial system to malignant disease.[66] Increased ferritin synthesis has been detected in peripheral blood lymphocytes from patients with Hodgkin's disease and this may also contribute to the elevated plasma ferritin levels.[67]

Detecting excess body iron in patients with refractory anemia

The plasma ferritin concentration is a useful clinical index of the amount of storage iron in patients with thalassemia. The concentration has been found to be directly related to the amount of blood given and to the iron concentration in liver biopsy tissue.[68] Measuring the plasma ferritin concentration has been help-

ful in detecting excess iron stores and in controlling iron therapy in anemic patients with chronic renal failure who are undergoing hemodialysis.[69,70] The results have indicated that many patients are given unnecessarily large maintenance doses of iron. While there is no proof that this does any harm, it seems prudent to avoid maintenance iron therapy in patients whose plasma ferritin levels are above the upper limit of normal.

Idiopathic hemochromatosis

Diagnosis: The plasma ferritin levels in these patients have been shown to correlate directly with the hepatic iron concentration, the urinary excretion of iron after the intramuscular administration of deferoxamine and the amount of iron mobilized by subsequent phlebotomy.[71,72] There are exceptions. Families have been encountered in which the plasma ferritin levels do not parallel the size of the iron stores.[73] This may be explained by the absence of stainable reticuloendothelial iron in the tissues of affected family members.[73] Families of this type appear to be uncommon.

The plasma ferritin concentration lacks specificity for the assessment of iron stores in patients with hepatocellular disease.[24] This creates diagnostic difficulty because iron overload may complicate advanced liver disease, especially when gastrointestinal bleeding has been minimized by the fashioning of a portacaval shunt.[74,75] In patients with hepatocellular disease the hepatic iron concentration has been found to correlate better with an empirical index derived from the ratio of the concentration of serum ferritin and serum glutamic oxaloacetic transaminase than with either concentration alone.[76] This implies that in patients with active hepatocellular disease the plasma ferritin level depends on both the size of the preexisting iron stores and the degree of hepatocellular damage. An extensive study of the diagnostic efficacy of tests for detecting iron overload in patients with chronic liver disease showed that the predictive value of a high result for transferrin saturation, plasma ferritin concentration, plasma ferritin/serum glutamic oxaloacetic transaminase ratio or iron absorption was less than 50% for any of these tests used alone or in combination.[77] On the other hand, the predictive value of a normal result for the exclusion of iron overload in patients with liver disease was 97% to 99% in a group with an assumed prevalence of iron overload of 10%. Hence, in patients with active hepatocellular disease and an increased plasma ferritin concentration or transferrin saturation or both, determination of the hepatocellular iron content of a percutaneous liver biopsy specimen is required to establish the presence of body iron overload.

Monitoring treatment: Plasma ferritin assays have been used to assess iron stores during the course of therapeutic phlebotomy for idiopathic hemochromatosis. Several groups have reported a progressive decline without large week-to-week fluctuations in the serum ferritin concentration.[76,78,79] In contrast, Leyland and colleagues[80,81] have reported widely varying serum ferritin concentrations during such therapy. They postulated that the variation might reflect the release of tissue ferritin components into the circulation during phlebotomy, because purified ferritin from the spleen, liver and heart of humans reacted with differing affinity in their assay system.

Early detection: Idiopathic hemochromatosis is inherited. Its early detection in relatives of affected individuals is important because phlebotomy will prevent clinical manifestations. Whereas diagnosis of the fully developed disease is not usually difficult, detection of early asymptomatic disease presents problems.

A comparison of the transferrin saturation and the concentrations of serum iron, plasma ferritin, chelatable iron in the urine and hepatocellular iron in patients with manifest hemochromatosis and their asymptomatic relatives suggested that, in the development of hemochromatosis, iron deposits first in the liver and later in other sites.[82] The plasma ferritin concentration does not appear to be a sensitive index of the hepatic iron concentration at this very early stage. A discrepancy between the plasma ferritin level and the amount of iron chelatable with deferoxamine suggests a relative decrease in ferritin synthesis during this phase.[34,71] This may be explained by the paucity of iron in reticuloendothelial cells.[83] Beyond this very early stage the plasma ferritin level appears to reflect the size of the iron stores.[82] In a study of 242 members of 43 families with idiopathic hemochromatosis Halliday and coworkers[84] found that increased iron stores were reflected in increased plasma ferritin concentrations in persons as young as 14 years whose hepatic iron concentration was at least twice the upper limit of normal. Moreover, the plasma ferritin concentration was increased before there was evidence of structural damage to the liver.

Since an increase in iron absorption is fundamental to the development of hemochromatosis, measurement of iron absorption should be a reliable test for the disease. The results have been disappointing, however, because values for iron absorption in patients with idiopathic hemochromatosis overlap the wide range of values in controls.[85] Better discrimination between patients with overt disease and controls was obtained when iron absorption was expressed in relation to the plasma ferritin concentration.[34,85] An investigation of a small number of families suggested that measurement of iron absorption may permit the detection of early idiopathic hemochromatosis in otherwise healthy relatives of persons with the disease.[86] Studies of additional families are required to establish the reliability of this method.

From a practical clinical standpoint measurement of the transferrin saturation and the plasma ferritin concentration is sufficient to identify family members with serious iron overload before tissue damage occurs.[77,84] Hepatic injury in the form of cirrhosis is associated with a transferrin saturation greater than 70% or a plasma ferritin concentration above the upper limit of normal for the appropriate age and

sex, or both. Abnormal results in either test warrants percutaneous liver biopsy to assess the hepatic iron concentration: a value above 250 μg per 100 mg of wet liver tissue in women or above 400 μg per 100 mg in men indicates serious iron overload.[82,87]

A new approach to defining family members at risk has come from studies of a linkage between the histocompatibility and hemochromatosis genes. The frequency of histocompatibility antigens HLA (human leukocyte antigen)-A3 and HLA-B14 in patients from France and HLA-A3 and HLA-B7 in patients from other countries, including Canada, has been found to be higher than expected.[88-90] Idiopathic hemochromatosis is determined by a locus closely linked to the A locus of the HLA complex on chromosome 6.[88] The pattern of transmission of the predisposing alleles in a pedigree, traced by typing for the A and B alleles of the HLA complex, is autosomal recessive.[90,91] Different antigens are involved in different families. Relatives who share both the HLA-A and HLA-B haplotypes with the proband are at risk of marked iron overload and clinical manifestations of the disease.[87,92] Relatives who have only one haplotype in common with the proband may have either no abnormality or minor iron overload. Their chance of having clinical manifestations appears to be small.[87]

HLA typing complements measurement of the plasma ferritin concentration and transferrin saturation for the early detection of hemochromatosis: HLA typing permits the identification of the hemochromatosis genotype — that is, the risk that iron overload will develop in family members, including a person with the disease. Biochemical tests such as plasma ferritin assays assess the phenotype or expression of this risk. For example, an HLA-identical sibling with an abnormal plasma ferritin concentration or transferrin saturation is at high risk; if the hepatic iron content is increased phlebotomy is warranted. An HLA-identical sibling with no biochemical abnormality of iron metabolism needs to have the plasma ferritin concentration measured regularly so that the size of the body iron stores can be monitored. This measurement, combined with the determination of genotypes, provides more precise information than was previously available for genetic counselling of family members. There is still a need, however, for an efficient test to detect carriers of hemochromatosis in the general population.

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