Clinical Applicability and Usefulness of Ferritin Measurements

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ABSTRACT

The accurate measurement of ferritin in the serum was first reported in 1972. Since then, the assay has become widely available to clinicians. However, the role of this assay in the diagnosis and treatment of various diseases is still poorly defined.

Serum ferritin levels are clearly useful in the diagnosis of simple iron deficiency. Hepatic disease, malignancies, and other chronic diseases can cause an elevation in serum ferritin which does not represent an elevation in body iron stores. While markedly elevated in late hemochromatosis, the value of serum ferritin in the detection of early hemochromatosis or the carrier state is not certain.

Introduction

Ferritin is the major storage form of iron in the body. It accounts for 15 to 30 percent of the total body iron and is second only to hemoglobin as the most abundant iron protein in the body.27,32,39 Ferritin has been found in all human tissues studied. Its principal locations are the liver, spleen, and bone marrow, with lesser quantities found in the heart, small intestine, placenta, kidney, and skeletal muscle.12,24,27,32

In 1972, serum ferritin was detected in normal human sera using a radioimmunoassay method.2 Since then much knowledge has been gained regarding the significance of the levels of circulating ferritin and its relationship to various disease states. The purpose of this paper is to review briefly the clinical aspects of serum ferritin measurements.

Function

In addition to its role as a store of iron, ferritin may play an important role in iron transport and intestinal absorption.25,50 Ferritin iron is in dynamic equilibrium with plasma iron.
Rapid changes in levels of circulating ferritin have been noted following venesection or experimental inflammation.\textsuperscript{30,37} The iron in ferritin is derived mainly from the heme of senescent red blood cells. Thus, radiolabelled ferritin is detected soon after the injection of \textsuperscript{59}Fe labelled red cells, but not after transferrin, hemoglobin-haptoglobin, or oral ferrous citrate.\textsuperscript{50} Most of the labelled ferritin is found in the liver.\textsuperscript{50,54}

Intestinal iron absorption in man is inversely related to body iron stores. One explanation is that the level of serum ferritin or mucosal cell ferritin is responsible for the changes in absorption. Raising the amount of circulating ferritin 100-fold in rats did not change their rate of intestinal iron absorption.\textsuperscript{25} The time interval between the ferritin infusion and the iron absorption measurement may not have been sufficient for a measureable effect to occur, however.

Structure

Ferritin consists of a protein shell, apoprotein, surrounding a central core of hydrous ferric oxide phosphate.\textsuperscript{12,18,27,28,32} The apoferritin portion has a molecular weight of about 450,000 daltons\textsuperscript{12,30,32,39} and is composed of 24 similar subunits, each with a molecular weight of about 18,000.\textsuperscript{12,32} Each ferritin molecule may contain up to 5,000 atoms of iron,\textsuperscript{12,27,32,39} although this is rarely achieved.\textsuperscript{27}

The most intriguing aspect of ferritin structure is the existence of isoferritins. It is now widely accepted that ferritin exists as a family of isoferritin.\textsuperscript{4,15,28,39,43,46} Gel electro-focusing reveals at least five isoferritins in most tissue. Furthermore, the isoferritin profile for each organ is quite specific.\textsuperscript{43} The heterogeneity of ferritin is due to the spectrum of hybrid molecules composed of differing proportions of the various subunit types.\textsuperscript{1,15,46} Since the subunits have different antigenic determinants, immunoassays of various ferritin types may yield spurious results.\textsuperscript{28,35,46,62}

Serum ferritin, like tissue ferritin, is heterogeneous and shares characteristics of liver and spleen ferritin.\textsuperscript{19} A question yet to be answered is whether serum ferritin represents the nonspecific release from damaged cells or secretion of specific isoferritin.\textsuperscript{15}

Synthesis

Iron has long been known to increase the synthesis of ferritin. This original observation by Granick\textsuperscript{24} has been confirmed by others.\textsuperscript{12,27,32,42} Neither Actinomycin D nor cycloheximide block the effect of iron in increasing the incorporation of amino acids into apoferritin.\textsuperscript{17,32} Drysdale and Shafritz conclude from this data that iron increases subunit release from polysomes and stabilizes completed ferritin molecules rather than increasing polypeptide synthesis.

Inflammation or fever is followed by an increase in ferritin levels. The increase in ferritin occurs before there are changes in the plasma iron or plasma iron turnover.\textsuperscript{20,37} The changes following inflammation are short lived.

Iron may also decrease the rate of ferritin breakdown.\textsuperscript{39,42} Iron rich ferritin has a longer half life than iron poor ferritin. Addition of iron, however, leads to synthesis of ferritin with a low iron content.\textsuperscript{20,32} Thus the role of iron in decreasing ferritin catabolism is still unknown.

Assay

The development of sensitive immunoassays has been the foundation for the study of serum ferritin. Prior to their development, ferritin in serum was detectable only in states where necrosis of cells released vast amounts of ferritin into the body.\textsuperscript{48} Ferritin was first detected in the sera of normal individuals by Addison in 1972.\textsuperscript{2}
There are two basic types of radioimmunoassays for serum ferritin,—the two site assay in which ferritin combines with a solid phase antibody, and the direct assay in which ferritin and antibody form a soluble complex.2,41

The two site assay has the advantages of being quite accurate at quite low ferritin concentrations and using reagents with a long shelf life.13,41 Modification of the direct assay, however, also yields reagents with a long shelf life.28 Other assays have been developed but have not seen wide use.14,62

It has been pointed out that the results of these assays depend on the serum isoferritin population, the isoferritin type of labelled ferritin, the specificity of the antisera, and the type of ferritin used as the standard.28

Normal Serum Ferritin

Much of the clinical usefulness of serum ferritin determinations relies on the association between body iron stores and serum ferritin. Serum ferritin concentrations are directly related to storage iron in healthy adults.32

The relationship has been most convincingly demonstrated by Walters.57,58 Iron stores were determined by quantitative phlebotomy, a very accurate measure of available iron. There was a strong correlation between the serum ferritin and the mobilizable iron.53 Each microgram per liter of ferritin corresponds to eight milligrams of tissue iron. The relationship between serum ferritin and tissue iron has been verified by studies of radioiron absorption,53,57 bone marrow aspiration3,8,40 and liver biopsy.38

Normal values for men are higher than for women. Normal values vary somewhat among laboratories, but generally the mean for adult males is 70 to 80 μg per L and for women, 30 to 50 μg per L.30,33,46,53,55 37,38,39,62 Some studies report higher values for men of 120–180 μg per L.3,22,32,48 The range of normal values is between 12 and 300 μg per L.20,46,58

Normal levels of ferritin in circulating blood cells (in fg per cell) are: red cells 0.025; polymorphonuclear leukocytes 6.6; lymphocytes 8.0 and monocytes 54.6.52

Iron Deficiency

The detection of iron deficiency is one of the most important uses of serum ferritin measurements. A high serum ferritin in the absence of inflammation or ineffective erythropoiesis effectively rules out iron deficiency.

Serum ferritin values in iron deficient patients average 4 to 8 μg per L.2,3,7,13,30,40 and a value below 12 μg per L denotes iron deficiency as defined on the basis of bone marrow iron, serum iron and transferrin levels.5,23,30,33,40,55

Ferritin levels are also useful in judging the effectiveness of iron therapy for iron deficiency.3 The ferritin may continue to rise in response to treatment even after a normal hemoglobin is attained indicating repletion of tissue iron stores.3 Patients with pernicious anemia often have increased ferritin levels. In this setting, a normal ferritin indicates concomitant iron deficiency and can be used to predict the development of iron deficiency after treatment of pernicious anemia.29

Studies in blood donors have shown that the donation of one unit of blood per year results in a decline in serum ferritin to one half of the pre-donation level. Women are more susceptible to the development of iron deficiency owing to blood donation.22 However, serum ferritin is of no help in predicting which donors will eventually develop iron deficiency.45

Iron deficiency in the presence of inflammation is difficult to diagnose since the serum iron is no longer a valid indication of iron deficiency.10 Serum ferritin levels also may not be a true index of iron stores in inflammation. This topic is discussed in the next section.
Chronic Disease

The anemia of chronic disorders was described by Cartwright and Lee as a normochromic or hypochromic anemia with a low serum iron and a low transferrin level and an increased reticuloendothelial iron which occurs in many infectious, inflammatory and malignant disorders. Serum ferritin levels are often elevated in the anemia of chronic disorders. This may represent a response to the disease itself and not elevated iron stores. The serum ferritin in chronic disease is not related to the duration, severity or type of inflammation present.

The value of serum ferritin measurements in detecting iron deficiency in the face of chronic disease is suspect. Most studies agree that a low serum ferritin in a chronic disease indicates iron deficiency but that a normal, or even increased serum ferritin does not exclude iron deficiency in chronic disease. In fact, only one third of all patients with inflammatory bowel disease and no stainable bone marrow iron had a serum ferritin level less than 18 μg per L. The value of serum ferritin measurements in chronic disease, therefore, is to confirm but not exclude, iron deficiency.

In a preliminary study, there is some evidence to show that the level of serum ferritin, even in anemia of chronic disease, is dependent on the amounts of iron stores rather than being an acute phase reactant. In patients with anemia of chronic disease but depleted iron stores, the average level of serum ferritin was 56 μg per L with a range of 2 to 170 μg per L. Whereas patients with repleted iron stores had an average ferritin level of 338 μg per L with a range of 100 to 2000, μg per L. The average serum ferritin level for simple iron deficiency was 16 μg per ml with a range of 1 to 60 μg per ml. There were 20 patients in each group.

Iron Overload

Hemochromatosis is a disorder characterized by excessive deposition of iron in parenchymal tissue. Idiopathic hemochromatosis is determined by a gene locus linked to the human leukocyte locus-A (HLA) complex. Phenotypic expression requires the presence of two hemochromatosis genes. There is a close correlation in hemochromatosis between serum ferritin and total body iron stores and hepatic iron concentration. Average serum ferritin concentrations are about 2000 to 3000 μg per L but values over 10,000 μg per L may be seen. The serum ferritin in idiopathic hemochromatosis is an acidic isoferritin which reacts well with liver ferritin antibody but not with spleen antibody.

Serum ferritin concentration may be used to monitor therapy in hemochromatosis. Patients treated by repeated phlebotomy will demonstrate a fall in serum ferritin. Studies involving serum ferritin have shed light on the biochemical basis of hemochromatosis. Serum ferritin is late to rise in hemochromatosis and does not reflect mobilizable iron stores as determined by quantitative phlebotomy or hepatic biopsy. It is proposed that there is an imbalance between chelatable iron and ferritin synthesis which may cause the high levels of intestinal iron absorption.

A subject of conflicting reports is the screening of relatives of hemochromatosis patients. Some groups consider serum ferritin a sensitive and specific screen for precirrhotic hemochromatosis. Others report cases of precirrhotic hemochromatosis with normal serum ferritin values. More recently, family studies using HLA typing to identify persons carrying the allele for the disease uncovered a small increase in serum ferritin in male heterozygotes over controls and quite sig-
significant differences between heterozygotes and homozygotes. These workers conclude that serum ferritin is the best indicator of disordered iron metabolism and it increases early in the course of iron overload.6

Malignancies

Serum ferritin levels may be elevated in various malignancies.11,13,21,31,34,36 The increase could be due to the presence of chronic disease with its attendant reticuloendothelial iron block, increased synthesis, and secretion of ferritin by tumor or tumor necrosis releasing ferritin into the serum.

In South African blacks with primary liver cancer, the mean serum ferritin was 845 μg per L. The serum ferritin level did not correlate with the liver iron content or with the aspartate amino transferase (SGOT).34 Powell et al interpreted this data such that the serum ferritin levels are not wholly secondary to the increased iron stores or hepatocellular necrosis.3

Serum ferritin and white blood cell ferritin is often elevated in hematologic malignancies.11,13,26,31,34,44,60,61 The serum ferritin level in acute myelomonocytic leukemia is 18 to 25 times normal; in acute myelogenous leukemia, it is six times normal; in acute lymphocytic leukemia, it is 13 times normal.11 The serum ferritin level correlates with both the number of blasts cells present and the serum muramidase level.61 Many patients with acute lymphocytic leukemia in remission and off of drugs have a normal serum ferritin. A high level may be a poor prognostic sign.51

Liver Disease

Serum ferritin levels are elevated in various types of liver diseases.13,23,48,62 Reissman, using a crude assay, was able to detect ferritin in the sera of patients with hepatitis and Hodgkin’s disease affecting the liver.49 Even at high levels the circulating ferritin did not contribute to the total serum iron.62 The mean ferritin levels in patients with all types of liver disease is 509 μg per L with a range of 32 to 3438 μg per L.49 The serum ferritin in liver disease is derived mainly from hepatocellular necrosis or injury. The serum ferritin generally does not correlate with liver function tests.49 Prieto et al report, however, that the ratio of serum ferritin to SGOT is a rough indication of body iron stores.48

Summary

Serum ferritin measurements are a quite recent addition to the diagnosticians’ armamentarium. Ferritin’s relation to iron stores in normal subjects is well established. Data are still being collected regarding their relation to various disease states.

Serum ferritin is useful in the diagnosis of simple iron deficiency. It is often used in the diagnosis of iron deficiency combined with chronic disease. The value of serum ferritin is unproven in the diagnosis of malignancy or early hemochromatosis.

Ferritin levels can be used as a guide to iron replacement therapy in iron deficiency. It is also useful in gauging the effectiveness of phlebotomy in hemochromatosis. Early suggestions that the serum ferritin may have prognostic significance in leukemia in remission await confirmation.

The development of more exact techniques and further data collection will surely broaden the application of serum ferritin measurements.

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