

## Guidelines for the Use of Serum Tests of Iron Stores

### 1. Background

Ferritin is the major storage protein for iron. It is present in virtually all cells where it sequesters iron in a soluble form providing accessible reserves for synthesis of iron containing compounds such as hemoglobin. It is present in particularly large amounts in macrophages and hepatocytes for storage and for metabolic purposes in erythroblasts. Although not a transport protein like transferrin, ferritin is present in small concentrations in the plasma which are directly proportional to the body's total iron stores. This relationship makes the serum or plasma assay for ferritin an ideal non invasive test of iron status.

Traditionally serum iron and the total iron binding capacity (TIBC) and the percent saturation, an indirect measurement of transferrin, have been used to determine iron status. A reduced level of serum iron *and* an elevated TIBC are required for a diagnosis of iron deficiency, whereas an increased proportion of saturation is suggestive of iron overload. (1)

### 2. Limitations

Levels of ferritin in the plasma are increased in acute and chronic inflammation as well as in certain malignancies such as Hodgkin's Disease. It is also elevated in hepatic cell damage which may make elevated levels difficult to interpret in hemochromatosis. An individual assay value must be interpreted with respect to any associated clinical conditions.

Plasma iron demonstrates substantial circadian fluctuations and day to day variations of as much as 30%. It can also be increased in inflammation, ineffective erythropoiesis and as a result of oral iron therapy. Transferrin, on the other hand, is reduced in inflammation, malignancies, liver diseases and malnutrition but is increased in pregnancy and as a result of oral contraceptives. These fluctuations in plasma levels unrelated to iron status can render the iron, TIBC and % saturation meaningless in many clinical situations. (2)

### 3. Alternative Tests

#### Iron Deficiency

The iron stain of an aspirated bone marrow particle is considered the gold standard for comparison of serum tests. However, on rare occasions it can provide a positive iron reaction although the patient is functionally iron deficient. These misleading stains tend to be associated with chronic inflammatory disease and the use of intravenous iron. Other tests, including free erythrocyte protoporphyrin, red cell ferritin and transferrin receptor have been used but do not demonstrate improved capabilities over the serum ferritin assay. (3)

#### Iron Overload

The definitive assay for increased iron stores is the iron content of a liver biopsy which is usually

obtained by the percutaneous or transjugular route. Non-invasive methodologies being used by specialist units include magnetic susceptometry and magnetic resonance imaging (MRI) but these techniques are only used to monitor accurately response to therapy and are not screening tests.

## **4. Indications**

### **Iron Deficiency**

The extremely high prevalence of iron deficiency in menstruating and pregnant females, adolescents and those on diets with poor iron intake along with the high sensitivity and specificity of the serum ferritin makes this the ideal diagnostic test. Levels will be decreased before there is a decrease in the mean red cell volume (MCV) or anemia. It has been suggested that the traditional cut off between deficient and normal be reconsidered (usually between 12 and 20 microgram/L) and that the statistical likelihood of iron deficiency does not decrease until values are > 40 microgram/L for uncomplicated populations and > 70 microgram/L for cases with inflammation or liver disease. (4)

Serum Iron, TIBC and % saturation, despite reduced specificity, will still be useful tests due to the high prevalence of deficiency. However, their value is considerably less in complicated situations and they add very little diagnostic value to the ferritin assay. For these reasons, it is not recommended that these tests be ordered in addition to ferritin in detection of iron deficiency.

A bone marrow aspiration and a stain of the particles for iron may be necessary in some cases.

### **Iron Overload**

Detection of iron overload is important to recognize due to the toxic effects of excess iron on the liver and heart in particular. Overload may occur due to hereditary hemochromatosis (present in 0.5 percent of North Americans) and in homozygous thalassemic conditions, part of which is due to the transfusional iron excess. (5) Screening for hemochromatosis requires measurement of transferrin saturation. If > 60% saturation in men or > 50% in women, a ferritin assay is the next step. If the ferritin is normal, repeat screening every two years is indicated. However, if ferritin is elevated, then further investigation by liver biopsy is warranted.

Interpretation of these screening tests requires caution. The serum ferritin generally reflects iron stores up to a level of 4,000 microgram/L. However, in a few cases of hemochromatosis the level may be a serious underestimate or even normal for no known reasons. The serum iron will be elevated, TIBC reduced and the % saturation increased in established cases but will provide no guide to the degree of overload. As with the ferritin, on occasions the % saturation will be erroneously normal for no obvious reason and sometimes levels will be affected by other complicating conditions described above.

A comparative study of the clinical usefulness of these tests looked at results from 1053 samples submitted to a reference laboratory from community and hospital patients. Although serum ferritin identified 239 cases of iron deficiency (23%), the serum iron and % saturation only identified 64 cases, all but four of which also had a low serum ferritin level. Physicians may have been ordering these tests for iron overload but only 131 cases had an increased % saturation, although 303 had elevated serum ferritin levels.

## 5. Interpretation

### *Tests to detect iron deficiency*

Serum ferritin	< normal range		iron deficiency, high degree of confidence
	< 40 $\mu\text{g/L}$		possible iron deficiency, lesser degree of confidence
	< 70 $\mu\text{g/L}$		iron deficiency in patients with inflammation, moderate degree of confidence
Serum Iron	decreased	}	iron deficiency, moderate degree of confidence
TIBC	elevated		
TIBC	normal		results are inconclusive

### *Tests to detect iron overload*

Serum ferritin	increased levels		reflect increased body stores
Serum iron	increased	}	increased stores but changes are not proportional to degree of overload > 60% in males, > 50% in females
TIBC	decreased or normal		
% saturation	increased		

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## 6. References

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## 7. Acknowledgements

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