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Unbound Iron Binding Capacity (UIBC) – An Alternative Lab Parameter for Iron Stores?

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Authors' contributions

This work was carried out in collaboration between both authors. Author UA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AS managed the analyses of the study and literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: Iron is a component of a number of proteins including haemoglobin, myoglobin, cytochromes and enzymes deficiency of which leads to iron deficiency anemia and excess in iron overload. There is a panel of tests to assess iron status in the body. A low serum iron & ferritin with an elevated TIBC are diagnostic of iron deficiency. While a low serum ferritin is virtually diagnostic of iron deficiency. AS ferritin is an acute phase reactant, it may not be a good marker for iron overload. The objective of the study was to find out whether UIBC is an alternative lab parameter of iron storage/ overload compared to ferritin.

Methodology: In a retrospective study conducted, data of 118 patients were collected, who were categorized as iron deficient and those with iron overload. Ferritin, UIBC and serum iron were assayed and remaining parameters were calculated.ROC curves were constructed using SPSS version 16 software.

Results: Area under the curve (AUC) for ferritin as a marker of iron storage, AUC for UIBC, serum iron, TIBC and transferrin were 0.108, 0.607, 0.098, 0.098 respectively. In patients with iron depletion, it was observed that AUC was 0.371 and 0.566 respectively for ferritin and UIBC respectively.

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Conclusion: Ferritin is a better marker of iron overload compared to UIBC, however, UIBC may be a better marker in iron store depletion. Entire iron panel if correlated and interpreted would be more useful in assessing iron stores.

Keywords: Ferritin; UIBC; transferring; iron; iron store.

1. INTRODUCTION

Iron is a component of a number of proteins including haemoglobin, myoglobin, cytochromes and enzymes involved in redox reactions. Hemoglobin is important for transport of oxygen to tissues throughout the body. Almost two thirds of the body's iron is found in hemoglobin in circulating erythrocytes [1]. About a quarter of the body's iron is found in readily metabolized stores as ferritin or hemosiderin in the liver and reticuloendothelial system. The remaining iron is in the myoglobin of muscle tissue and a variety of enzymes necessary for oxidative metabolism and other cell function. The iron content of the body is highly conserved. To achieve iron balance, adult men need to absorb about 1 mg per day and adult menstruating women about 1.5 mg per day, although this is highly variable. Inadequate intake can lead to varying degrees of deficiency, from low iron stores (as indicated by low serum ferritin and a decrease in iron-binding capacity), to early iron deficiency and iron deficiency anemia. Iron overload results in hemochromatosis.

Serum iron is carried by binding protein, transferrin. Total Iron Binding Capacity (TIBC) is a test that measures the blood's capacity to bind iron with transferrin. It is a measure of the maximum amount of iron that it can carry, which indirectly measures transferrin [2] since transferrin is the most dynamic carrier. TIBC is less expensive than a direct measurement of transferrin [3,4]. Normally, only about one third of iron binding sites of transferrin are occupied by iron. So serum has considerable reserve iron binding capacity.This is called as serum unsaturated iron binding capacity (UIBC).The UIBC is calculated by subtracting the serum iron from the TIBC. Transferrin saturation is calculated from serum iron and UIBC, is used in the diagnosis of iron overload.

Ferritin is a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion. Ferritin is found in most tissue as a cytosolic protein, but small amount are secreted into the serum where it functions as an iron carrier. Plasma ferritin is also an indirect marker of the total amount of iron stored in the body; hence serum ferritin is used as a diagnostic test for iron deficiency anemia [5]. However it is not very specific marker for iron stores.

As ferritin is an acute phase reactant which is elevated in various inflammatory conditions, may not be an ideal marker for iron store. Unbound iron binding capacity (UIBC), which is s-total iron binding capacity (2 times s-transferrin) minus s-iron could be a better marker for diagnosing empty/ excess iron stores.

Iron deficiency anemia is a most common disorder which occurs mostly in women of pre-menopausal age. It occurs mostly in women of rural areas who are suffering from poverty. Most of them are suffering from malnutrition, which is a primary cause of development of iron deficiency anemia. The secondary cause of iron deficiency anemia is excess blood loss during menstrual cycle. Iron overload, known as hemochromatosis indicates accumulation of iron in the body, may be due to genetic or acquired causes.

Iron deficiency anemia is one of the most widespread diseases all over the world. In India 5-6% of general population suffers from this disease. It is prevalent in 3% among men & 10-14% among women. In specific groups like slum dwellers, plantation laborers & pregnant women the prevalence rate is 30-50% or even more.

A low serum iron & ferritin with an elevated TIBC are diagnostic of iron deficiency. While a low serum ferritin is virtually diagnostic of iron deficiency, a normal serum ferritin can be seen in patients who are deficient in iron & have coexistent diseases (Hepatitis, anaemia of chronic disorders).The test findings are useful in distinguishing iron deficiency from other microcytic anaemia's.

It has been proved that Ferritin is a marker of inflammation rather than iron status in overweight and obese people. Complete iron profile including transferrin, rather than serum ferritin alone, can truly predict iron deficiency in such people [6]. So it is justifiable to look for a better marker for iron store.

Asberg et al reported that, for diagnosing empty iron stores UIBC is a better marker of iron stores [7]. There are not many such studies in Indian settings to the best of our knowledge.

1.1 Objective

To find out whether UIBC may be used as an alternative lab parameter of iron storage/overload compared to ferritin

2. METHODOLOGY

2.1 Study Design

Type of study: Retrospective study

Study setting: Clinical Biochemistry, KS Hegde Medical Academy, Mangalore

Study population: Data of 118 patients who underwent sampling for iron profile testing at Clinical Biochemistry laboratory, suffering from iron deficiency anaemia (microcytic hypochromic) with Hb<10 gms or iron overload, transferrin saturation of more than 45% were selected. Institutional ethics committee approval was obtained. Serum ferritin level of above 250 ng/ml in premenopausal women and above 300 ng/ml in postmenopausal women and men were considered as iron overload patients.

Iron store depletion was studied in 31 patients with ferritin levels less than 30 ng/ml.

Exclusion criteria: Patients on iron supplementation, Serum iron and UIBC were estimated by using Roche, Cobasc311, Ferritin by Cobas e411. Serum iron, serum transferrin and serum transferring saturation were calculated by using suitable formulas.

Normal reference range for ferritin was 29-248 ng/ml, serum iron 60-150 µg/dl, TIBC 250-400 µg/dl in our laboratory.

Study period: Data was collected over a time period of 4 months,January –April 2018.

Data analysis: The data was analyzed using the software SPSS 16. The entered data was verified and checked for data errors during coding and data entry.

Statistical tests used: ROC curve analysis was done to compare the diagnostic accuracy of iron, sransferrin and UIBC. Empty iron stores were defined as ferritin less than 10 µg/L .

3. RESULTS

It was observed that 39 patients had iron overload and 79 patients were not suffering from iron overload. Receiver operating characteristic (ROC) was constructed for each parameter. Area under the curve (AUC) for ferritin as a marker of iron storage was 0.998 as shown in Fig. 1. AUC for UIBC, serum iron, TIBC and transferrin were 0.108, 0.607, 0.098, 0.098 respectively (Figs. 2-4).

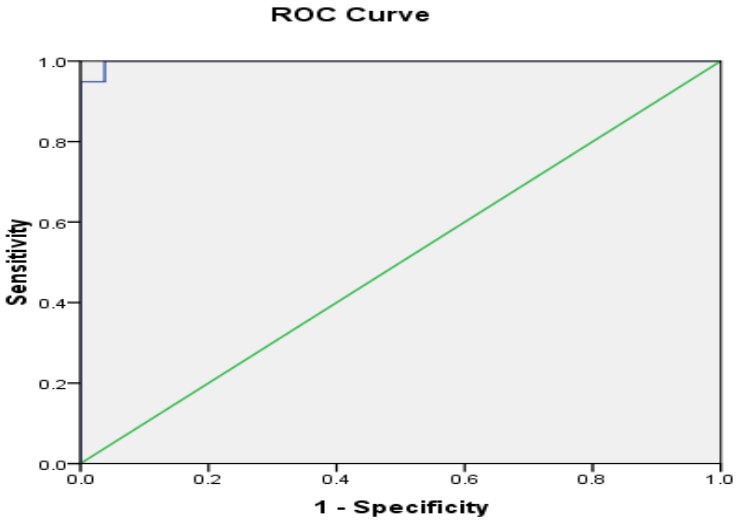

Fig. 1. ROC curve for ferritin as a marker of iron overload

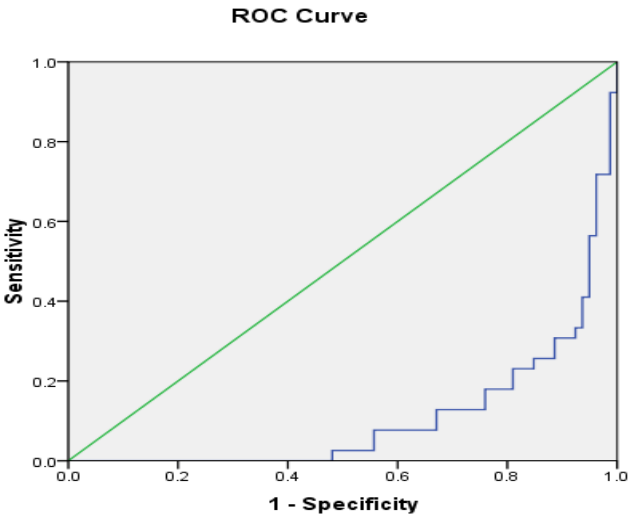

Fig. 2. ROC curve for UIBC as a marker of iron overload

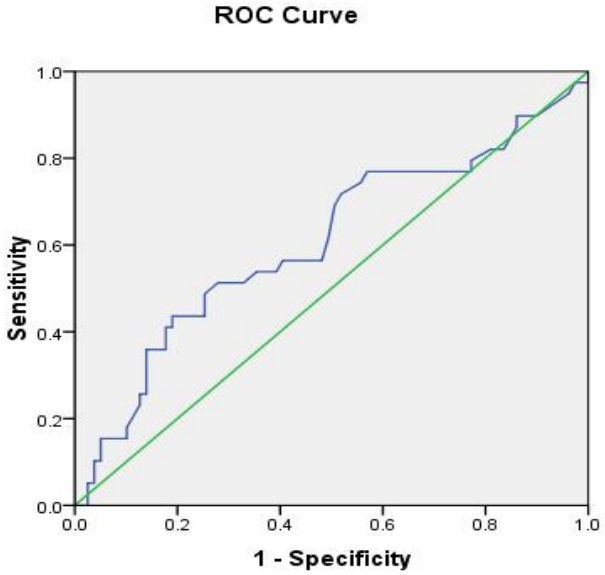

Fig. 3. ROC curve for serum iron as a marker of iron overload

When we considered 31 patients with iron depletion,it was observed that AUC was 0.371 and 0.566 respectively for ferritin and UIBC in iron store depleted patients (Figs 5 & 6).

4. DISCUSSION

Ferritin is the intracellular storage form of iron. As ferritin is an acute phase protein, it may rise in inflammation, liver disease, and malignancy[8]. In these patients, ferritin can appear falsely elevated or normal, when actually stores are low. Serum iron refers to ferric ions (Fe3+) bound to serum transferrin. Serum iron concentration is highly variable and is affected by dietary iron intake, inflammation, and infection [9]. Transferrin is the principal iron transport protein in plasma. It increases in iron deficiency to maximize utilization of available iron [8].

Total iron binding capacity is an alternative test to transferrin. TIBC reflects the availability of iron binding sites on transferrin. Values increase in iron deficiency and decrease in iron overload. Unsaturated iron binding capacity (UIBC) can be assayed and TIBC can be calculated by adding serum iron to UIBC.

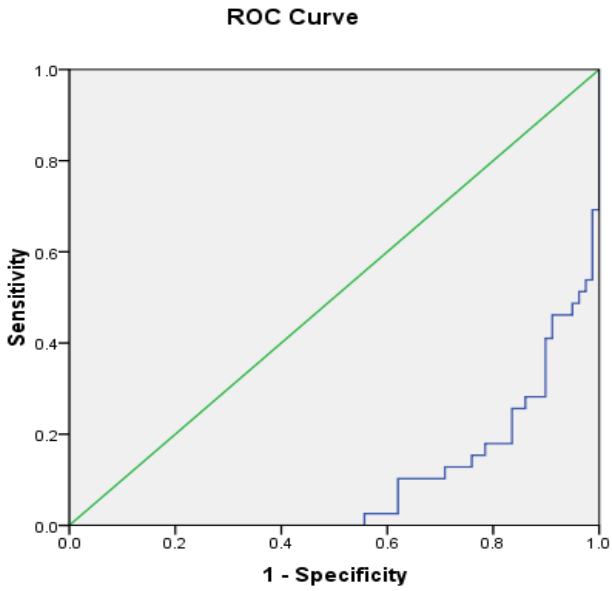

Fig. 4. ROC curve for TIBC and serum tranferrin, as a markers of iron overload

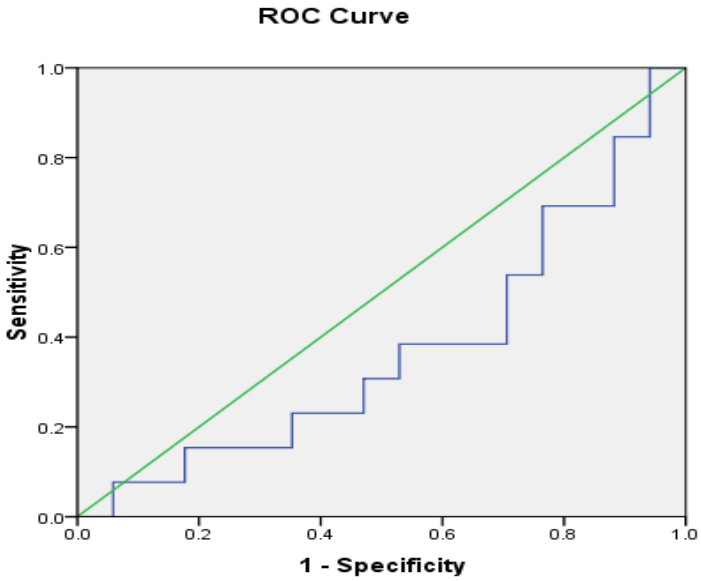

Fig. 5. ROC for ferritin as a marker of iron store depletion

Transferrin saturation is calculated from serum iron and either TIBC or transferrin measurements. Typically, transferrin is 30% saturated with iron [9]. Transferrin saturation rises in iron overload and falls in iron deficiency, but does not quantitatively reflect iron stores [10]. A rise in serum iron due to dietary iron intake can cause raised transferrin saturation.

Interpretation of iron studies can be challenging and affect almost all markers of iron status. Nevertheless, iron studies play an important role in clinical assessment.

It has been found in an unselected population that, raised serum ferritin (>200 µg/L for premenopausal women or >300 µg/L for men and postmenopausal women) and transferrin saturation >50% diagnosed C282Y homozygosity with a sensitivity of 90% in men and 75% in women [11]. In marked hyperferritinemia (>1000 µg/L) or for further

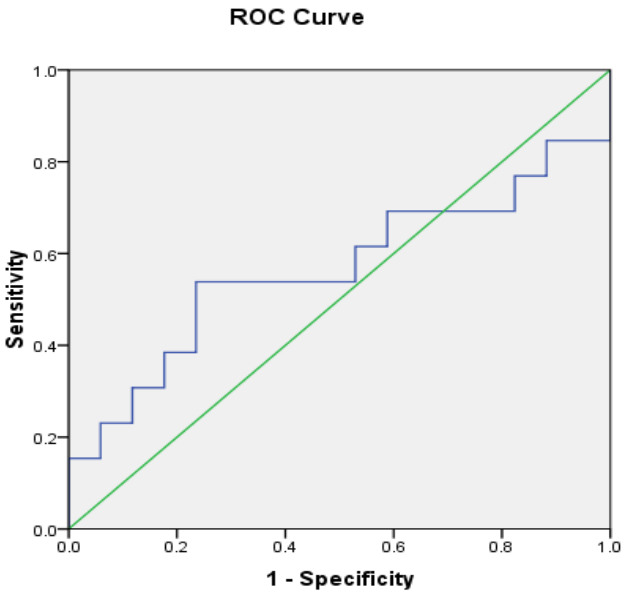

Fig. 6. ROC for UIBC as a marker of iron store depletion

assessment when the diagnosis of iron overload is in doubt, special techniques like liver biopsy, magnetic resonance imaging etc are required for assessing iron overload [10]. However they are not widely available and are usually requested by specialists. Low serum ferritin (<15 µg/L) provides absolute evidence of iron deficiency [12].

The accuracy of the test depends on how well the test can differentiate those with the disease and without the disease. The accuracy of the test is determined by the area under the ROC curve. AUC of 0.9- 1 suggests an excellent test, 0.8-0.9 good and 0.7- 0.8 represent a fair test. AUC value below 0.7 is unacceptable. Based on these criteria, it was found in our study that ferritin is an excellent marker for iron overload, whereas other markers are not acceptable (Fig 1-4). ROC of ferritin, as well as UIBC, suggest that both the markers may not be accurate in diagnosing iron store depletion separately (Figs. 5 & 6).

On contrary to our result, Luke et al suggested that transferrin saturation and UIBC have equal reliability inability to predict hemochromatosis. The study suggests that UIBC should be considered as an alternative to transferrin saturation in the detection of hemochromatosis [13]. Hickman et al suggested that automated measurement of unsaturated iron binding capacity enables a cost-effective, large-scale population screening programme for C282Y hereditary haemochromatosis [14].

Our results suggest that UIBC is a better marker (AUC = 0.566) compared to ferritin (AUC= 0.371) in iron depletion. However, both the results were not in the acceptable range. Asberg et al opined that, at all definitions of empty iron stores s-UIBC had a better diagnostic accuracy than the other tests, with an area under the ROC curve of 0.85-0.97. When diagnosing empty iron stores calculation of s-UIBC is a better way to utilize the information in serum iron and transferrin than the calculation of transferrin saturation [15].

From the above discussion, it has been evident that none of the markers alone are ideal to assess the iron status. So serum ferritin and transferrin saturation together should be used to assess for iron overload, alongside haemoglobin to assess iron status.

5. CONCLUSION

It is concluded from our study that ferritin is better marker of iron overload compared to UIBC, however UIBC may be a better marker in iron store depletion. Entire iron panel if correlated and interpreted would be more useful in assessing iron stores.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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