An analysis of the cost and clinical effectiveness of the laboratory tests for Iron studies including deficiency (Anaemia) and overload (Haemochromatosis): The district general perspective.

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Abstract

Background: Screening for Iron deficiency or overload is done by checking Serum Ferritin, Iron, and Transferrin saturations. Iron deficiency is investigated with endoscopy and serology for coeliac disease and Iron overload (Hereditary Haemochromatosis) by C282Y genetic test.

Aims and Objectives: To validate the cost effectiveness of tests recommended for making the diagnosis of Iron deficiency or overload.

Methods: All serum samples received in a sample district laboratory of UK for full one year with requested serum Ferritin, Iron level and Transferrin saturation were analysed in retrospect for cost effectiveness. As a second step analysis was made of those who had C282Y genetic test for Iron overload.

Results: Total of 28133 samples were sent in one year for Ferritin and found low in 0.8% while high in 16.1%. Serum Iron and Transferrin saturation were checked in 1770 samples. Serum Iron level was found low in 22.9% and high in 2.4%. Transferrin saturation was low in 51% and high in 3.4%. Total 41 patients were tested for C282Y genetics, 43.9% samples had no mutation, 34.1% were heterozygous carriers and 21.9% had a confirmed homozygous mutation.

Conclusion: It cost the district with 150,000 populations, £53,394 for laboratory tests. It included 23 carriers or sufferers of hereditary hemochromatosis. Checking Serum Iron and Transferrin were not useful in Iron overload. Serum Ferritin was more useful in screening for Iron overload but less helpful in Iron deficiency. Transferrin saturation was twice more sensitive than Iron level in indicating Iron deficiency in our data.

Keywords: Bariatric surgery, Gastric banding, Resting metabolic rate, Ghrelin, Leptin.

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Introduction

Baseline Iron studies are commonly conducted by the doctors and nurses for either Iron deficiency or Iron overload. A lot of cost is involved in both; doing the basic screening tests, and then tests that are subsequently indicated according to findings of Iron deficiency or an overload. The basic tests include serum Iron level, Transferrin level, Transferrin saturation, and serum Ferritin as a base line. In patients with Iron deficiency, if there is no other systemic cause for Iron deficiency, then usually gastroscopy and colonoscopy, are undertaken. Serum serology for coeliac disease using IgA Tissue Transglutaminase is also done. When Iron overload is suspected, genetic tests like C282Y for Hereditary Haemochromatosis are undertaken sometimes accompanied by Liver Biopsy and measurement of Liver Iron load. Most cases of raised Ferritin level however are due to inflammatory response of Liver and in these cases CRP and other inflammatory markers may be raised. Alcohol excess and steatohepatitis are common causes of a raised serum Ferritin level.

Common causes of Iron deficiency include non-gastrointestinal reasons like menorrhagia in women, silent haematuria etc. Gastrointestinal causes include acid peptic disease, GI malignancies, coeliac disease, inflammatory bowel disease and nutritional problems.

Commonest iron overload condition seen is Hereditary Haemochromatosis (HH). This is an autosomal recessive condition characterized by normal iron-driven erythropoiesis and toxic accumulation of iron in the parenchymal cells of the liver, heart and endocrine glands. The disorder was first observed by Trousseau in 1865 [1], and more fully described by Sheldon in 1935 [2]. It is caused by reduced activity of Hepcidin, a protein regulating the entry of iron to the blood-steam [3]. The most common form of GH is due to an HFE gene mutation, on the short arm of chromosome 6 [4], resulting in a cysteine to tyrosine conversion at amino acid 282 (C282Y). This is found in approximately 90% of HH patients [5]. Homozygosity for the trait occurs in approximately 5 per 1000 north European Caucasians [6]. Non-HFE Haemochromatosis syndromes share the same phenotype, however are due to mutations in other genes such as Hepcidin (HAMP), Haemojuvelin (HJV), Ferroportin (FPN), Transferrin receptor 2 (TFR2). These can be found in the non-Caucasian population [7].

Though several genetic modalities have been described, they share a common pathogenesis of increasing the iron load in the
blood to more than is required for erythropoiesis. This causes an increase in the saturation of transferrin, and deposition in multiple organs throughout the body. The resultant diseases present in middle age and feature cirrhosis, hypogonadism, diabetes, cardiomyopathy, arthropathy and skin pigmentation [8]. The spectrum of disease of HFE-related haemochromatosis varies from abnormal biochemical markers to severe organ damage and disease. This spectrum exists as C282Y HFE homozygosity only predisposes patients to haemochromatosis; additional host or environmental factors are required to develop disease.

Transferrin saturation levels are raised in early disease, and progress to raised ferritin levels indicating accumulation of iron in tissues [9]. The European Association for the Study of the Liver (EASL) recommends measurement of fasting transferrin saturation and serum ferritin in a patient with suspected iron overload. HFE testing should be performed only in those who have a raised transferrin saturation (>45% in females, >50% in males) [10].

In the presence of a raised serum ferritin with no other causes (alcohol, inflammation, cell necrosis, metabolic syndrome) assessing the fasting transferrin saturation is recommended. If these are raised on 2 samples then the patient should proceed onto genotyping of the HFE gene.

In our laboratory, serum ferritin levels are raised when >300 μg/l in men and post-menopausal women and >200 μg/l in pre-menopausal women. Genotypic testing will identify those homozygous for C282Y and those heterozygous for C282Y who have an increased risk of iron accumulation.

**Aim of the Study**

This study aims to evaluate the burden of cost and clinical effectiveness of basic diagnostic tests done for iron disorders either Iron deficiency or Iron overload. These include serum Iron, Transferrin, Transferrin Saturation and Ferritin levels. As results of these basic tests then lead to further investigations like gastroscopy, colonoscopy, and genetic testing for C282Y genes, the study also aims to indicate areas of potential savings. The study is a real-world snap shot of practice in a health area in the UK. It is not a study of screening an entire population of the country but a sample large district of UK.

**Methods**

All serum samples received in a sample district laboratory of UK (Grantham District Hospital) for full one year (from 1st April 2015 to 31st March 2016) with a requested serum ferritin, iron, Transferrin and Transferrin saturation were identified and included in this retrospective study. Grantham is a large and mainly rural district with a catchment of 150,000. Requests for above blood tests came from all sources including the general practitioners, primary care health workers, secondary care nurses and the doctor at the hospital. Serum samples came from all medical and surgical sub-specialities including gastroenterology, haematology, general internal medicine and emergency medicine. Paediatric samples were excluded from the study. Sample identification was done if coded for Ferritin, Transferrin saturation, or Serum Iron level in hospital database. As a second analysis those coded for C282Y genetic test were identified from the hospital database and their results were analysed individually. Whether the sample came from a patient already known to have iron deficiency, overload, haemochromatosis, any family history of haemochromatosis or the indication for doing the test was not known so the recruitment was blind. All tests were done in the same laboratory with standardised controls and normal values were taken as Ferritin 275, Transferrin saturation 20-55%, Iron 5.8 - 34.5 and C282Y negative.

**Statistical Analysis**

Data was collated on an excel spread sheet, exported and analyzed using SPSS. As it is a service development study, ethics approval was achieved through the local clinical governance and audit department. Local Information Technology department helped to identify cases from the database. This study is looking at results of laboratory tests in anonymous manner and aiming to find cost effectiveness of the tests, hence it did not require direct patient involvement. The outcome measures are informed by patients’ priorities, experience, and preferences as understandably, patients would want blood tests to be cost effective and clinically beneficial. The results of the study have a potential to change practice and benefit patients.

**Results**

Total of 28133 serum samples were sent to laboratory in one year for analysis of Ferritin, Transferrin saturation, or Iron level in our sample district. Of this, 21207 (76.4%) samples were sent through primary care while 6926 (24.6%) were submitted by various hospital specialists. Serum Ferritin level was requested in all 28133 serum samples but Transferrin saturation and Iron level were checked in 1770 samples only (Table 1).

Serum ferritin levels were found below normal in 213 (0.8%), higher than normal but less than twice normal in 2871 (10.2%), more than twice normal but less than thrice in 1249 (4.4%) and more than thrice normal in 394 (1.4%). Serum Ferritin level was therefore normal in 83.1% while lower than normal in 0.8% and higher than normal in only 16.1%.

Therefore the proportion of samples with high ferritin level that could lead to suspicion and further investigations for haemochromatosis was small (16.1%) yet it is a more sensitive indicator for investigation of Iron overload provided inflammation is excluded. However we did not correlate it to inflammatory markers like CRP and did not have history of Alcohol intake or fatty liver as data collection was blind.

Serum iron and transferrin saturation were checked in 1770 samples. Serum Iron level was found normal in 1323 (74.7%) while it was low in 405 (22.9%) and high in only 42 (2.4%). Transferrin saturation was normal in 807 (45.6%), low in 902 (51%) and high in only 61 (3.4%).

**Table 1. Samples of serum iron and transferrin saturation.**

<table>
<thead>
<tr>
<th>Percentage level</th>
<th>Ferritin</th>
<th>Serum Iron</th>
<th>Transferrin Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>16.1</td>
<td>2.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Normal</td>
<td>83.1</td>
<td>74.7</td>
<td>45.6</td>
</tr>
<tr>
<td>Low</td>
<td>0.8</td>
<td>22.9</td>
<td>51.0</td>
</tr>
</tbody>
</table>
Hence it was extremely rare to find either high Iron levels or high Transferrin saturation in samples tested by us. It is also noted that low Iron levels were found in 22.9% samples but Transferrin saturation was low in 51% almost twice as frequently (Table 1).

We were unable to determine how many patients with Iron deficiency actually went on to get gastroscopy, colonoscopy or coeliac serology tested. For Iron overload however 41 samples were tested for C282Y genetic tests. Of these 39 had raised Ferritin level above normal, but despite having low serum Ferritin level, 2 proceeded to get genetic tests. Of the 41 patients tested for C282Y genetics, 18 (43.9%) samples had no mutation, 14 (34.1%) were heterozygous carriers and 9 (21.9%) had a confirmed homozygous mutation.

It cost the district £42199.50 for serum Ferritin, £955.80 for Iron levels, £4088.70 for Transferrin saturation and £6150 for C282Y genetic test. Therefore it cost the sample district with a population of 150,000 a total of £53,394 for laboratory expenditure excluding sample collection costs. This picked 23 carriers or sufferers of Hereditary Haemochromatosis (iron overload) and maximum 902 cases of Iron deficiency.

**Discussion**

Our data has shown that it is not very common to find high readings for Transferrin saturation (3.4%) or Iron levels (2.4%) in laboratory tests done for these. The usefulness of these two tests for checking Iron overload has not been substantiated in our study. Serum Ferritin is much more often raised (16.1%) and therefore seems more useful in primary screening for Iron overload.

In our study the situation is found much different when looking for Iron deficiency where low levels are more frequently detected for both serum iron (22.9%) and Transferrin Saturation (51%). However Serum Ferritin level seems to be less helpful in checking for Iron deficiency (0.8%).

This study has further indicated that in cases of Iron deficiency the Serum Transferrin saturation seems more often reduced (51%) compared with Serum iron level (22.9%). This implies that Transferrin saturation was twice more sensitive than Iron level in indicating Iron deficiency in our data.

The strengths of this study are that; we recruited samples from multiple hospital specialists as well as the general practitioners in the community, all samples submitted in a year were recruited and number of samples is large. There are no such previous studies that have analysed the clinical and cost effectiveness in this manner. The study is however based in only one district of the UK and can be therefore biased by practices of local medical personnel. More studies involving other districts are warranted. Other limitations of the study include no information on the confounders for ferritin like weight, inflammation etc that may have improved the ascertainment of iron overload versus other causes of elevated ferritin. Also there is no information on whether the tests were ordered for initial diagnosis, monitoring of therapy, family screening and all these are relevant to the choice of testing conducted. However, the study is a real-world snap shot of practice in a health area in the UK and simply reports the yield of diagnosis for C282Y homozygosity, high ferritin, low ferritin, high and low Serum Iron and Transferrin saturations in samples sent for measurement.

In our data 16% of samples had a high Ferritin yet identification of iron overload by genetic testing is rare. Ferritin level was more than twice normal but less than thrice in 1249 and more than thrice normal in 394. Thus at least 1643 patients had raised Ferritin level at more than twice normal but only 41 had C282Y tests done. Confirmatory tests that would be useful in this group include CRP, lipid profile, ESR etc. to exclude other causes of raised Ferritin which our data did not correlate with. Not knowing how many patients had confirmatory tests debars us to entirely exclude an under appreciation of the presence of Hereditary Haemochromatosis in our data and this limitation is acknowledged.

**Conclusion**

Two messages are however clearly obvious from this study. Firstly that Ferritin is a better marker of Iron overload if inflammatory process and alcohol is excluded and a poor marker of Iron deficiency. Secondly that Serum Iron and Transferrin saturation are poor markers in Iron overload but better markers in Iron deficiency, particularly Transferrin saturation being twice as sensitive.

There is therefore a need for the authorities to give further guidance on the matter. Many questions warrant answers. Should Iron level be measured at all as it seems less useful in both deficiency and overload, although slightly better indicator in deficiency than an overload situation? Can Transferrin saturation measurement alone be good enough a test for Iron deficiency? Further studies are warranted to compare measurement of Transferrin saturation alone versus in combination with serum Iron levels in making diagnosis of Iron deficiency and its cost effectiveness. Furthermore, should serum Ferritin be measured at all if Iron deficiency is suspected? Future guidance is also needed on when to suspect Iron overload. Further studies are also warranted on knowing real value of measuring serum Iron or Transferrin saturations if Ferritin level is high and inflammation, alcohol or liver inflammation have been excluded. Our study indicates that there is potential for cost savings if future studies answer some of the above questions and authorities guide us further. Meanwhile more studies and guidance are urgently required.

**References**


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