VALUE OF SERUM TRANSFERRIN RECEPTOR LEVELS IN ASSESSING IRON STATUS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE


ABSTRACT

Background: It is difficult to assess iron status in patients with chronic inflammatory conditions such as inflammatory bowel disease (IBD). Currently available tests including serum ferritin and transferrin saturation have limitations in differentiating Iron Deficiency Anaemia (IDA) from Anaemia of Chronic Disease (ACD). Serum soluble transferrin receptor (sTfR) level has been proposed as a potential tool to identify iron deficiency in patients with chronic inflammation. sTfR levels are not influenced by inflammation and high levels are thought to represent iron deficiency.

Methods: The aim of our study was to examine the value of sTfR in the assessment of iron status in patients with IBD. The study comprised of 154 patients with IBD, diagnosed on clinical, endoscopic, histological and/or radiological findings. They were compared with age and sex matched healthy controls (n=209). All patients and controls had blood investigations comprising haemoglobin (Hb), serum B12, red cell folate, ferritin, transferrin, serum iron and sTfR. Iron deficiency was considered to be present in anaemic patients (IDA group) if both ferritin and serum iron levels were low, < 15 ug/l and < 10 micromol/l respectively. Anaemic patients with normal or raised ferritin combined with either normal or low serum iron were classified as having ACD. Serum soluble transferrin receptor levels were measured by enzyme linked immunoassay from Orion Diagnostica.

Results: Of the 154 patients, 61 patients were found to be anaemic based on the Hb thresholds as described above. A subgroup of 44 patients was

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classified as iron deficient (IDA) based on low ferritin or iron. 17 of the 61 anaemic patients were found to have a normal ferritin and serum iron. sTfR levels were not significantly different in the patients in the IDA group (n=44) 2.59 +/- 1.48 mg/l compared with either patients in the ACD group (with normal ferritin and serum iron) (n=17) 1.67 +/- 0.77 mg/l (P>0.05) or with IBD patients without anaemia (n=93) 1.62 +/- 0.78 mg/l (P>0.05). These results were also not significantly different to healthy controls (n=209) 1.55 +/- 0.60 mg/l.

Conclusions: Anaemia is common in patients with inflammatory bowel disease. There were no significant differences in the sTfR levels in patients with inflammatory bowel disease irrespective of iron status compared with healthy controls. The early promise of sTfR as a useful tool in differentiating iron deficiency anaemia from anaemia of chronic disease has not been confirmed.

INTRODUCTION

It is difficult to assess iron status in patients with chronic inflammatory conditions such as inflammatory bowel disease (IBD) (1) and is particularly so when iron deficiency coexists with anaemia of chronic disease. Currently available tests such as serum ferritin have limitations in differentiating iron deficiency anaemia (IDA) from anaemia of chronic disease (ACD) (1,2). The main limitation of a single measurement of serum iron to determine iron status is its physiological variability with an effective within subject coefficient of variation of around 30%. Small changes in supply and demand can lead to rapid changes in serum iron concentration. Low serum iron does not necessarily indicate an absence of iron stores.

A diurnal rhythm has been reported with higher values in the morning than in late afternoon. Most of the iron in plasma is bound to transferrin (10-30 umol/l; mean 20umol/l) and less than 1 umol/l exists in unbound form as ferric citrate.

Serum ferritin levels normally correlate closely with iron stores. However, serum ferritin can be raised in patients with liver disease and levels may be raised in inflammatory disorders in spite of iron deficiency as part of the acute phase response. In ACD iron transfers from haemoglobin to reticuloendothelial stores and this will be reflected in serum ferritin levels whereas serum iron will tend to fall in ACD.
Serum soluble transferrin receptor (sTfR) level has been proposed as a potential tool to reliably identify iron deficiency in patients with chronic inflammation (2,3). sTfR is not an acute phase protein and will not rise with inflammation and high levels are thought to represent iron deficiency. In patients with Rheumatoid Arthritis (RA) transferrin receptor numbers in erythroblasts are reduced (4) and sTfR levels in anaemic patients with RA were found to be normal as opposed to patients with iron deficiency anaemia where the levels were found to be raised.

METHODS

The aim of our study was to examine the value of sTfR in the assessment of iron status in the patients with inflammatory bowel disease in a West London population.

The study comprised of 154 patients with IBD between the age range 17-90 years, diagnosed on clinical, endoscopic, histological and/or radiological findings. 95 of the 154 patients had Ulcerative Colitis, 41 had Crohn’s Disease and 18 were classified as Indeterminate Colitis. They were compared with age and sex matched healthy controls (n=209) from the same local community. All patients and controls underwent blood investigations comprising haemoglobin (Hb), serum B12, red cell folate, ferritin, transferrin, serum iron and sTfR. Anaemia was defined in these patients as a haemoglobin level of less than 11.5 in females and 13.5 in males. Iron deficiency was considered to be present if the ferritin was < 15 microg/l and the serum iron was < 10 micromol/l. Anaemic patients with normal or raised ferritin combined with either normal or low serum iron were classified as having ACD. Serum soluble transferrin receptor levels were measured by enzyme linked immunoassay from Orion Diagnostica.

RESULTS

Of the 154 patients, 61 patients were found to be anaemic based on the Hb thresholds as described above. These patients with anaemia did not have any deficiency in their serum B12 or red cell folate levels. A subgroup of 44 patients was classified as iron deficient (IDA) based on low serum ferritin and serum iron. 17 of the 61 anaemic patients were found to have a normal or high ferritin. STfR levels were not significantly different in the patients in the IDA group (n=44) 2.59 +/- 1.48 mg/l compared with either patients in the ACD group (n=17) 1.67 +/- 0.77 mg/l (P>0.05) or with IBD patients without anaemia (n=93) 1.62 +/- 0.78 mg/l (P>0.05). These results were also not significantly different to healthy controls (n=209) 1.55 +/- 0.60 mg/l.
DISCUSSION

Anaemia is common in patients with inflammatory bowel disease. There were no significant differences in the sTfR levels in patients with IBD irrespective of iron status compared with healthy controls. The early promise of STfR as a useful tool in differentiating iron deficiency anaemia from anaemia of chronic disease has not been confirmed.

The failure of sTfR to reliably identify iron deficiency in the IDA group makes it clinically unhelpful in determining iron status in patients with iron deficiency co-existing with anaemia of chronic disease or in patients with normal haemoglobin but incipient iron deficiency.

Hepcidin is considered to be the central humoral regulator of iron homeostasis and is thought to play an important role in anaemia of chronic disorder (5,6). Hepcidin binds to ferroportin in the duodenum reducing iron export from the enterocyte (7).

Whenever erythropoiesis is accelerated TfR1 expression in erythroblasts will increase inversely corresponding to the reduction in cellular iron levels. The higher transferrin receptor expression will in turn create greater demand for iron resulting in decreased diferric transferrin levels. The lower diferric transferrin levels would then be detected by the HFE/TfR1 complex and Transferrin Receptor 2 (TfR2) in the liver (8, 9). This signalling process would result in reduction in hepcidin expression and increased iron absorption in enterocytes.

Intestinal absorption of dietary ferrous iron is mediated by two iron transport proteins. Dietary iron is transported into the enterocytes by the luminal surface transporter divalent metal ion transporter 1 (DMT1). The enterocyte basal transporter is ferroportin and exports iron from the enterocyte to plasma.

Transferrin bound iron is taken in by in the bone marrow by the classical transferrin receptor 1 (TfR1) pathway. The excess iron is stored in the liver by a mechanism which includes TfR2 expression.

Anaemia of chronic disorder is thought to be due to up regulation in the liver of the peptide Hepcidin by cytokines IL1 and IL6 leading to reduced iron absorption from the gut and decreased iron release from macrophages in the
reticuloendothelial system (7, 10). Additionally erythropoietin production is impaired and erythroid precursors respond poorly to erythropoietin and red cell survival is decreased mildly (10, 11).

The HFE protein in Haemochromatosis is analogous to major histocompatibility complex (MHC) molecules and requires beta2 microglobulin for surface presentation. The Cys 282 Tyr substitution in HFE disrupts the association with beta2 microglobulin and prevents surface presentation of HFE. Therefore Hepcidin upregulation fails in patients with Haemochromatosis in spite of iron overload. TfR2 also plays an important role in iron metabolism in addition to Hepcidin (12).

Serum ferritin is mostly derived from macrophages. Ferritin genes (13) encode for a regulatory sequence in the ferritin mRNA termed the iron regulatory element (IRE). When cell iron concentrations rise the IRE binding to cellular iron regulatory proteins (IRP) is disrupted and ferritin synthesis proceeds and in iron overload high ferritin levels are seen and the converse occurs in iron deficiency states (14). The rise in serum ferritin seen with chronic inflammation is attributed to anti-inflammatory Th2 cytokines such as IL 10. (15) Cellular Fe levels also control transferrin receptor expression via the IRE-IRP binding mechanism.

In IDA in the background of chronic disease the serum sTfR levels appear to increase in patients with rheumatoid arthritis. (16,17) but a single value of sTfR was found to be of limited value in determining iron storage in any individual with RA (18).

Most of the body pool of TfR is in erythroid cells (19,20) and circulating reticulocytes contribute significantly to serum sTfR levels (19). Shedding of sTfR is constitutively mediated by a member of the metalloprotease family known as ADAM (a disintegrin and metalloprotease) (21).

Our study suggests the interesting possibility that shedding of transferrin receptors by erythroblasts is inhibited in IBD patients irrespective of iron status. This would provide an explanation for the similar sTfR levels found in IBD patients with and without iron deficiency.

REFERENCES


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