IRON DEFICIENCY ANAEMIA

Soluble Transferrin Receptors - A New Marker for Iron Deficiency

GENERAL

Hypochromic microcytic erythrocytes are characteristic of iron deficiency anaemia, but these cells also occur in cases of longstanding anaemia of chronic disease, haemoglobinopathies (thalassaemia and other haemoglobin abnormalities such as Haemoglobin C), congenital sideroblastic anaemia and lead poisoning.

Although iron deficiency is classified as a nutritional deficiency anaemia, its main cause is chronic blood loss. Even in vegetarians, in the absence of blood loss, iron deficiency anaemia is rarely found.

The main source of human iron intake is red meat. Iron absorption takes place in the duodenum and depends on gastric acid. The latter ensures that iron is available in the absorbable, ferro form (Fe2+). In the circulation iron is transported by transferrin and stored as ferritin.

Toddlers (due to growth) and women in their reproductive years (due to menstruation) have a negative iron balance, i.e. only sufficient for normal haemopoiesis. Any disturbance in this regard will therefore cause them to be iron deficient.

If an iron deficiency is suspected, the diagnosis should be confirmed and the cause of the deficiency be determined prior to commencement of treatment.

SOLUBLE TRANSFERRIN RECEPTORS – A NEW MARKER FOR IRON DEFICIENCY

DEFINITION

Soluble transferrin receptors occur in the circulation and are shortened fragments of the transmembrane transferrin receptor formed by splitting the transmembrane receptor.

FUNCTION

The transferrin receptors bring about the intracellular uptake of iron. Serum soluble transferrin receptor is a quantitative determination of the functional iron status and reflects the availability of iron at tissue level.

MECHANISM OF FUNCTION

The transferrin receptor is expressed on all body cells that require iron, therefore its highest concentrations occur in the cells of organs with the highest iron need, such as the erythroid bone marrow and placenta.

The circulating iron transferrin complex binds with the transferrin receptor in the cell membrane. Consequently intracellular absorption of iron takes place and transferrin is again released into the circulation.

HOW ARE SOLUBLE TRANSFERRIN RECEPTORS REGULATED?

The concentration is regulated according to the intracellular iron content and its individual
Iron needs. Iron deficient cells have an increased number of receptors and iron overloaded cells have a reduced number of receptors. The concentration of secreted receptors in serum (i.e. soluble transferrin receptors) correlates with the total receptor content of the cells.

**REDUCED WITH:**
- Reduced erythropoiesis, e.g.
  - Aplastic anaemia,
  - Bone marrow ablation for stem cell transplant.
- Iron overload.

**INCREASED WITH:**
- Microcytic anaemia as a result of iron deficiency
- Increased erythropoiesis such as haemolytic anaemia and recent blood loss.
- Ineffective erythropoiesis such as myelodysplastic syndromes and megaloblastic anaemia.
- Microcytic anaemia as a result of sideroblastic anaemia or thalassaemia.

**DIAGNOSTIC VALUE OF SOLUBLE TRANSFERRIN RECEPTORS**
- **Mainly for the differential diagnosis of microcytic anaemia in order to distinguish between anaemia of chronic disease and iron deficiency anaemia.**
- Conventional methods, for example ferritin, are not always able to distinguish between the two, with the result that a bone marrow aspiration has to be performed in order to evaluate the body's iron stores and make a definitive diagnosis.
  - In the case of iron deficiency, tissue and serum transferrin receptors are increased, but when anaemia is secondary to inflammatory conditions the receptors do not increase. Ferritin, however, may be normal or increased.
  - If iron deficiency anaemia and anaemia of chronic disease occur together, the receptors will still be increased.
  - When the body's iron stores are exhausted, transferrin receptors increase even before changes can be detected in the other accepted markers of iron deficiency, namely transferrin saturation, MCV (erythrocyte mean cell volume) and erythrocyte protoporphyrin concentrations.
- Transferrin receptors are especially valuable in cases where the determination of serum ferritin provides limited information about the body's iron balance, namely in pregnant women, neonates, adolescents in their rapid growth phase, athletes, transplant patients and malignancies.
- Iron deficiency in the presence of acute inflammation in which case the ferritin may be increased.
- Monitoring of iron therapy: The soluble transferrin receptors increase earlier than
haemoglobin and ferritin levels.

- In chronic renal failure: If soluble transferrin receptors are increased, and ferritin is normal/reduced, patients will not respond to erythropoietin since there is a concomitant iron deficiency.
- For the prediction of response to erythropoietin treatment: If the transferrin receptors rise 20% above the baseline within 2 weeks after initiation of erythropoietin treatment or dosage increase, an early prediction of response seems likely.

**ADVANTAGES OF DETERMINING SOLUBLE TRANSFERRIN RECEPTORS**

- The test requires very little serum (10ul), therefore these receptors are also suitable for paediatric patients.
- It provides the same information in respect of iron content as can be gained from a bone marrow aspiration, but is non-invasive.

**SERUM SOLUBLE TRANSFERRIN RECEPTOR INDEX**

It is a mathematical relationship between serum soluble transferrin receptor and serum ferritin determinations and is even more accurate than the aforementioned in confirming the diagnosis of iron deficiency.

**NORMAL REFERENCE RANGE**

The normal reference range is approximately 6% higher in Black patients than in patients of Caucasian origin and is approximately 6% lower at sea level.

**DIAGNOSIS OF IRON DEFICIENCY**

It is important to distinguish between iron deficiency anaemia and anaemia of chronic disease.

The diagnostic approach towards iron status is based on the determination of three iron pools, namely the metabolic, storing and transport pools respectively as well as the soluble transferrin receptor and index.

- **METABOLIC POOL - HAEMOGLOBIN AND MCV (ERYTHROCYTE MEAN CORPUSCULAR VOLUME)**
  - This refers to the erythrocyte haem iron.
  - The FULL BLOOD COUNT shows a hypochromic microcytic anaemia with or without a reactive thrombocytosis.

- **STORAGE POOL - SERUM FERRITIN, BONE MARROW STAINING FOR IRON**

  Ferritin: Reduced, but since it is an acute-phase protein, it may be falsely normal or even increased. The body iron store is depleted before the haemoglobin starts dropping and the red cells become hypochromic microcytic. During the first phase of an iron deficiency the blood picture may therefore be normal.

  Bone marrow: Prussian blue staining of bone marrow particles provides the most accurate information about the body iron stores, but this method is not normally used.
to evaluate iron stores. It is however indicated when sideroblastic anaemia is suspected.

- **TRANSPORT POOL - SERUM IRON, SERUM TRANSFERRIN AND PERCENTAGE TRANSFERRIN SATURATION**

  Serum iron is usually decreased in the case of iron deficiency and inflammatory conditions. Serum transferrin increases in iron deficiency and decreases in inflammation. Percentage transferrin saturation is decreased in iron deficiency.

- **DETERMINATION OF SERUM-SOLUBLE TRANSFERRIN RECEPTOR AND INDEX**

  Increased levels of soluble transferrin receptor and index point to iron deficiency (even if haemoglobin and MCV are still normal), and they provide the same information with regard to iron status as a bone marrow examination.

<table>
<thead>
<tr>
<th>s-Fe</th>
<th>% s-TfS</th>
<th>s-Tf</th>
<th>s-FER</th>
<th>s-STfR</th>
<th>s-STfR index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Deficiency</td>
<td>↓/N</td>
<td>↓</td>
<td>N/↑</td>
<td>±↓</td>
<td>↑</td>
</tr>
<tr>
<td>Chronic Disease</td>
<td>↑/N</td>
<td>↓/N</td>
<td>↓/N</td>
<td>N/↑</td>
<td>N</td>
</tr>
<tr>
<td>Chronic Disease with iron deficiency</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>↑</td>
</tr>
</tbody>
</table>

  s-Fe: serum iron
  % s-TfS: percentage serum transferrin saturation
  s-Tf: serum transferrin
  s-FER: serum ferritin
  s-STfR: serum soluble transferrin receptor
  s-STfR indeks: serum soluble transferrin receptor index (serum STfR/log serum ferritin)
  ↓: reduced
  N: normal
  ↑: increased
  ±: low normal
  Var: variable

Since the serum iron can fluctuate over a period of 24 hours, it is not accurate as a single test. Serum iron is also influenced by diet. Only a fasting specimen is therefore recommended. The serum ferritin determination can however be used on its own, but may be "falsely" increased. Serum soluble transferrin receptor and index are able to establish the diagnosis of iron deficiency when the other markers may be unreliable.

**GUIDELINES FOR THE CONFIRMATION OF IRON DEFICIENCY - IN ORDER OF SIGNIFICANCE**

a) Full blood count
b) Iron studies, namely serum iron, transferrin, % transferrin saturation and ferritin
c) Soluble transferrin receptors and soluble transferrin receptor index (see uses)
d) Iron staining of bone marrow particles
TREATMENT OF IRON DEFICIENCY

The cause of iron deficiency has to be treated first of all; otherwise the treatment with Fe will be ineffective. If parenteral iron preparations are used, the dosage should be calculated according to the formula set out in the package insert of the product.

If oral iron preparations are used, they should contain enough elemental iron (between 150 and 200 mg daily). Each dosage for an adult should contain between 50 and 100 mg elemental iron. Side effects such as abdominal discomfort, nausea, constipation and a black colouring of stool can be reasons for rather starting with a lower dosage.

Treatment should continue for not less than six months, after which the patient should be re-evaluated with a full blood count, serum ferritin, serum soluble transferrin receptor and index determinations.

The reticulocyte count starts increasing after approximately one week and the haemoglobin count after two weeks. The serum soluble transferrin receptor and index decreases even earlier. The response time for oral and parenteral iron administration is virtually the same, except in case of malabsorption. Vitamin C administration could accelerate the absorption of iron. Ferro salts should be taken 1 hour before meals and not together with antacids. Combination medicines (iron in combination with vitamins or minerals) should preferably be avoided.

EXAMPLE

Fe $\text{SO}_4$ 200 mg tablets contain 66 mg elemental iron. Initiate therapy with 1 tablet a day for one week, increase by 1 tablet per week to a maximum of 1 tablet three times daily by the third week. For the duration of the first month 2 tablets can be taken three times a day, 500 mg Vitamin C per day could be added.

Depending on the degree of anaemia, the iron store in the bone marrow and the serum ferritin are usually increased in megaloblastic anaemia. If this is not the case, an underlying iron deficiency is very likely, and this combination often gives rise to normocytic anaemia.

IN SUMMARY

It is possible to categorise and diagnose the development of an iron deficiency in different phases:

<table>
<thead>
<tr>
<th>Earliest subclinical phase. Depleted iron stores</th>
<th>Decreased serum ferritin</th>
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<tr>
<td>↓</td>
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<tr>
<td>Followed by a reduction of the transport pool</td>
<td>Serum iron and % serum transferrin saturation decrease whilst serum transferrin increases</td>
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<tr>
<td>↓</td>
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<tr>
<td>Later a tissue iron deficiency develops</td>
<td>Serum soluble transferrin receptor and index increases</td>
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<tr>
<td>Eventually a clinical iron deficiency develops</td>
<td>Microcytic anaemia develops</td>
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<tr>
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<td>Haemoglobin and MCV erythrocyte protoporphyrin increases</td>
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