Understanding Iron Deficiency Anaemia in Chronic Kidney Disease

Information at Advanced Level. Karen Jenkins RN, PGDip HE, MSc

Learning outcomes

1. Understand markers used to define iron deficiency anaemia in chronic kidney disease
2. Understand types of iron deficiency and when to treat
3. Gain knowledge and understanding of the medicines available to treat iron deficiency in chronic kidney disease
4. Understand how guidelines can be used in practice

Introduction

Iron deficiency is a public health problem and the most common and widespread nutritional disorder in the world. A deficiency of iron leads to a reduction of the normal physiological function of tissues in the blood, brain, and muscles. This can be detected by the symptoms of iron deficiency anaemia such as fatigue, breathlessness, deterioration in concentration and reduced exercise tolerance. The onset is often insidious and the symptoms can be similar to those experienced in chronic kidney disease (CKD) itself, diabetes and heart disease.

Iron deficiency anaemia (IDA) is common in people with CKD, particularly those with stage 3B, 4 and 5 CKD and in patients with both diabetes and CKD. Reduced iron levels in CKD can be caused by:

- Bleeding (Patients with CKD have a tendency to bleed due to platelet dysfunction)
- The inability to absorb iron from food
- The demand made on iron stores by the use of erythropoiesis stimulating agents.
- Haemodialysis blood loss

The causes of IDA which apply to the general population can also apply to people with CKD and should not be excluded when investigating IDA. These include:

- Dietary iron deficiency
- Gastrointestinal disorders
- Infectious diseases e.g. malaria, tuberculosis
- Acquired immunodeficiency syndrome (HIV/AIDS)
- Haematological disorders e.g. thalassaemia
- Blood loss

As iron has an essential role in the process of myoglobin and haemoglobin synthesis and lack of iron leads to a reduction in the function of tissue in the brain, muscles and blood.

There are five stages of IDA

- Normal iron status (normal iron indices)
- Latent iron deficiency (reduction of iron stores)
- Iron depletion (no iron stores)
- Iron deficient erythropoiesis (reduced iron transport)
- Iron deficiency anaemia (microcytic, hypochromic anaemia)

Adequate iron stores are required to support the process of erythropoiesis. As red cell production increases, iron stores decrease and therefore need to be maintained. (150mg iron is required to raise haemoglobin by 1g/dl). 65% of iron stored in the body is used to form haemoglobin. If there are inadequate iron stores red cell survival is reduced. In people without CKD normal red cell survival is 120 days, in CKD it is ~ 90days.

Markers used to define Iron deficiency in CKD

There is ongoing debate as to the most accurate test to use to measure iron status. WHO recognise that prevalence of iron deficiency has been derived from the prevalence of anaemia related to haemoglobin measurements. It is important to note that not all people with anaemia are iron deficient and that iron deficiency can occur without anaemia.

A variety of tests can be used to diagnose IDA:

- Full blood count;
  - red cell indices
  - mean corpuscular volume (MCV)
  - mean corpuscular Hb Concentration (MCHC)
  - mean corpuscular haemoglobin (MCH)
- Serum ferritin
- Serum % transferrin saturation
• Serum iron  
• Total iron binding capacity (TIBC)  
• Transferrin  
• % Hypochromic red cells  
• Nutritional status  
• Gastrointestinal blood loss assessment

The most common tests used or assessing iron status in CKD are

- Serum ferritin  
- % Transferrin saturation (TSAT) levels  
- % Hypochromic red cells

These are explained in detail in the next section.

Serum ferritin

Serum ferritin is an indicator of iron storage but not of iron supply, it is an acute phase reactant and its levels are affected by inflammation. As cytokines are commonly increased in CKD, serum ferritin levels might not reflect true iron stores. If this is suspected, C reactive protein (CRP) levels should be measured at the same time to confirm the presence of infection or inflammation. Serum ferritin results should be treated with caution and repeated when the infection/inflammation subsides. Serum iron levels should also be noted.

The units used to measure Serum ferritin are µg/L or ng/ml. The normal range can vary between laboratories. A reduced serum ferritin level <30ng/ml (30µg/L) is indicative of iron deficiency.

Levels at which to maintain serum ferritin vary depending on which guideline is used in your area of practice. The section on guidelines will discuss the parameters which can be applied to people with CKD both with and without dialysis.

% Transferrin Saturation

%Transferrin saturation (% TSAT) refers to the transport system of iron. Transferrin fluctuates due to the diurnal variation of serum iron and is affected by nutritional status, leading to a lack of sensitivity and specificity in assessing iron’s availability. Although commonly used it is not a very reliable marker as it constantly changes. Therefore more than one measurement is needed to ascertain an average reading.

% Hypochromic Red cells

The measurement of Hypochromic Red cells and reticulocyte haemoglobin content is a direct assessment of the incorporation of iron into erythrocyte haemoglobin, giving an estimate of the recent functional availability of iron into the erythron. This test can be a more accurate marker than serum ferritin or transferrin saturation.

Hypochromic red blood cells (HRC) tend to have less colour than normal red blood cells and increase in number when iron stores are insufficient and/or mobilization of iron is inadequate. 2.5% of red cells are normally hypochromic. Red blood cells are hypochromic if they have a haemoglobin concentration of < 280 g/L. A HRC level greater than 10% is an indication of iron deficiency.

N.B. This test is not available in all laboratories.

Types of Iron Deficiency

There are two types of iron deficiency

- Absolute iron deficiency  
- Functional iron deficiency

Absolute Iron deficiency

This is when there are inadequate iron stores available to support the erythropoietic needs of the bone marrow, i.e. not enough iron stores to make the required amount of haemoglobin. It can be caused by: insufficient dietary intake, poor absorption in the gut or blood loss.

It can be defined as a serum ferritin, level < 100µg/L, and/or % Transferrin Saturation level < 20% or Hypochromic red cells > 6%.

Functional Iron Deficiency

This is when there are sufficient iron stores but the iron is not readily available to meet the demands of erythropoiesis i.e. it doesn’t reach the bone marrow fast enough. The most common test used to define functional iron deficiency is transferrin saturation (TSAT). A normal TSAT is 20-40%.

Functional iron deficiency is defined by normal (30-200µg/L) or raised serum ferritin levels (>800 µg/L), % Transferrin saturation < 20% or % hypochromic red cells > 6%.

Table 1 is a summary of Absolute and Functional IDA

<table>
<thead>
<tr>
<th>Absolute Iron Deficiency</th>
<th>Functional Iron deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron stores inadequate to support the erythropoietic needs of the bone marrow</td>
<td>Iron stores adequate but cannot supply marrow quickly enough with the iron required to support demands of erythropoiesis when stimulated acutely (e.g. with ESA therapy)</td>
</tr>
<tr>
<td>Defined as serum ferritin &lt;100µg/L</td>
<td>Defined by normal (30-200µg/L) or raised serum ferritin levels (&gt;800 µg/L)</td>
</tr>
<tr>
<td>% Transferrin saturation&lt;20%</td>
<td>% Transferrin saturation &lt; 20%</td>
</tr>
<tr>
<td>% Hypochromic red cells&gt;10%</td>
<td>% Hypochromic red cells &gt; 10%</td>
</tr>
</tbody>
</table>
Medicines used to treat iron deficiency anaemia

Choosing Iron supplementation

KDIGO\textsuperscript{12} suggest the route of administration of iron supplementation for adults with CKD, not receiving Haemodialysis (HD) be based on:

- Severity of IDA
- Availability of venous access
- Response to previous use of oral iron
- Side effects of previous oral or IV iron therapy
- Patient adherence
- Cost
- Whether or not receiving ESA therapy
- Patient’s overall clinical status

If a trial of oral iron is unsuccessful intravenous (IV) iron can be considered based upon iron status tests (Ferritin, %TSAT, %HRC) to achieve the optimum Hb level to be attained.

UK guidelines (NICE)\textsuperscript{13} recommend people receiving ESA maintenance therapy should be given iron supplementation to maintain:

- Serum ferritin levels 200-500µg/L in both HD and non HD patients
- and either %TSATS >20% or %HRC < 6% unless ferritin >800µg/L

NICE\textsuperscript{12} opinion is that in practice this is likely to require the use of IV iron supplementation.

Studies carried out in patients with CKD not receiving dialysis\textsuperscript{14,15} suggest a small efficacy advantage of IV, compared with oral administration of iron with a mean Haemoglobin difference of 0.31g/dl (3.1g/L) However, while these studies indicated IV iron significantly increased serum levels of ferritin and TSAT, haemoglobin levels were not consistently raised. The choice of iron supplementation will ultimately depend on clinical need and fulfilling the aim to manage and treat IDA effectively.

Oral Iron

As there are several preparations of oral iron available, the decision which to use is usually based on by the tolerability of side effects, frequency of administration and patient choice. The daily amount needed to treat IDA is approximately 200mg of elemental iron per day\textsuperscript{16}. Table 2 illustrates the elemental iron content of three commonly used oral iron supplements and related therapeutic doses\textsuperscript{17}.

The side following side effects of oral iron often affect adherence to treatment

- Gastric irritation
- Nausea
- Constipation, (more common in the elderly population)
- Diarrhoea, more likely in patients with inflammatory bowel disease.
- Dark colouring of stool

It is also important to remember that oral iron can interact with some medicines commonly used in CKD. See Table 3

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Type of Interaction and action required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids or medicines containing sodium bicarbonate, aluminium, magnesium, zinc</td>
<td>Reduced oral absorption of iron. Ensure medicine taken 2-3 hrs apart.</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Reduced oral absorption of both medicines. Ensure medicine taken at least 30 minutes to 1 hr apart.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Reduced oral absorption of both medicines. Ensure medicine taken 2-3 hrs apart.</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Chelation, reduced oral absorption of both medicines. Ensure medicines taken at least 2-3 hrs apart.</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Reduced oral absorption of levothyroxine. Ensure medicines taken at least 2-3 hours apart.</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Reduced oral absorption and decreased antihypertensive effect. Ensure medicines taken at least 2 hours apart. *may require an increase in methyldopa dose.</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Reduced oral absorption of penicillamine. Ensure iron is taken at least 2 hours after penicillamine dose.</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Reduced oral absorption of both medicines. Ensure medicines taken at least 3 hours apart..</td>
</tr>
<tr>
<td>Zinc</td>
<td>Reduced oral absorption of both medicines. Ensure medicines taken at least 2-3 hours apart.</td>
</tr>
</tbody>
</table>

Table 2 Therapeutic Dosing of Oral Iron

<table>
<thead>
<tr>
<th>Iron Salt</th>
<th>Amount</th>
<th>Content of Elemental iron</th>
<th>Therapeutic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumerate syrup*</td>
<td>140mg/5ml</td>
<td>45mg</td>
<td>10-20 mls x 2 per day</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>300mg</td>
<td>35mg</td>
<td>300mg 4-6 x per day</td>
</tr>
<tr>
<td>Ferrous Sulphate</td>
<td>200mg</td>
<td>65mg</td>
<td>200mg 2-3 x per day</td>
</tr>
</tbody>
</table>

* Ferrous Fumerate is often used for patients with swallowing difficulties
Patients not receiving haemodialysis may receive oral iron either as a prophylactic or as a continuation of maintenance therapy after initial correction with intravenous iron an example of prophylactic dosing of oral iron can be seen in Table 4.

Table 4 Prophylactic Dosing of Oral Iron

<table>
<thead>
<tr>
<th>Oral Preparation</th>
<th>Dose/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Sulphate</td>
<td>200mg once daily</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>300mg x 2 daily</td>
</tr>
</tbody>
</table>

Intravenous Iron

The use of IV iron supplementation for patients receiving haemodialysis has been common practice for many years. Although a meta-analysis by Rozen et al\(^{18}\) demonstrated that 60% of people with CKD not having haemodialysis can achieve their aspirational Hb target and maintain it by IV iron repletion alone, i.e. without additional use of ESA therapy, the use of IV iron in practice varies. This may be due to several factors:

- Practicalities of administration
- Access to resources
- Availability of preparation (e.g. on hospital formulary)
- Cost of preparation
- Availability of Venous Access
- Patient choice

A review by The European medicines Agency (EMA) in June 2013\(^{19}\) highlighted the risk of serious allergic reactions following the administration of IV iron containing medicines, especially in pregnant women. Recommendations from the review have implications for the administration of IV iron for renal patients, in particular those who have home haemodialysis. The EMA (2013) state that iron preparations should only be given in an environment where resuscitation facilities are available, by staff who have been trained to evaluate and manage anaphylactic and anaphylactoid reactions. This is to ensure that patients who develop an allergic reaction can be treated immediately. This ruling means that patients are no longer able to give IV iron themselves at home. This has been common practice in the UK for some time. This change means patients will now have to go to their nearest renal unit to receive IV iron therapy. The EMA also commented on the use of test doses. They no longer advocate the administration of a test dose due to data indicating that allergic reactions may still occur in patients who have not reacted to a test dose. Product SPC’s may need to be amended if this recommendation is made permanent.

There are several preparations of IV iron with different methods of administration e.g. divided bolus doses or single dose infusion. See Table 5. This list is not exhaustive and other preparations may be available worldwide.

The following side effects are common with the administration of IV iron\(^{16}\)

- Taste disturbances
- Nausea
- Vomiting
- Abdominal pain
- Diarrhoea
- Chest pain
- Headache
- Dizziness
- Flushing
- Fever
- Myalgia
- Arthralgia
- Hypotension
- Bradycardia
- Tachycardia
- Hypersensitivity reactions
- Injection site reactions

Table 5 IV Iron Preparations

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Max dose Bolus</th>
<th>Frequency of bolus</th>
<th>Maximum Single Dose Infusion</th>
<th>Rate of Infusion</th>
<th>Test Dose required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmofer® (Iron (III) Hydroxide dextran complex)</td>
<td>200mg</td>
<td>Max 3 per week</td>
<td>20mg/kg</td>
<td>4-6 hrs</td>
<td>Yes</td>
</tr>
<tr>
<td>Ferinject ® (Ferric Carboxymaltose)</td>
<td>1000mg</td>
<td>1-2 per week</td>
<td>1000mg</td>
<td>15 mins</td>
<td>No</td>
</tr>
<tr>
<td>Monofer® (Iron Isomaltoside)</td>
<td>200mg</td>
<td>3 per week</td>
<td>20mg/Kg</td>
<td>Up to 1 hour</td>
<td>No</td>
</tr>
<tr>
<td>Rienso® (Ferumoxytol)</td>
<td>510mg</td>
<td>2-8 days apart</td>
<td>510mg</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Venofer® (Iron Sucrose)</td>
<td>200mg</td>
<td>3 per week</td>
<td>200mg</td>
<td>30 mins</td>
<td>Yes</td>
</tr>
<tr>
<td>Ferrllicit ®(Sodium Ferric Gluconate complex) HD Only</td>
<td>125mg</td>
<td>Daily in HD</td>
<td>125mg</td>
<td>Up to 1 hour</td>
<td>Yes</td>
</tr>
</tbody>
</table>
- Peripheral oedema
- Paraesthesia
- Fatigue
- Anaphylactoid reactions

Contraindications for the use of IV iron include:
- History of allergic disorders such as asthma and eczema
- Infection
- Active rheumatoid arthritis
- Previous allergic reaction to iron therapy

Cost Implications of Treating IDA

Oral Iron

This is by far the cheapest option. It can be self administered at home, does not require an additional clinic or hospital appointment, is easily accessible and can be prescribed by the patients GP.

IV Iron

The cost of and availability of the drug can influence how an IV iron service is run. Economic factors will play an important part in service development particularly in regard to any reimbursements made for the administration of the drug. A comparative cost analysis of three types of IV iron preparations, including drug cost, nursing time, equipment and patient transportation examined the comparative cost to the health economy of IV iron supplementation options including blood transfusion. A blood transfusion cost the most followed by multiple small doses of IV iron. A single does infusion of IV iron proved to be the most cost effective overall. Drug costs will vary from country to country, and although oral iron will be the cheapest available treatment it is not necessarily the most effective for people with CKD.

Guidelines - application to practice

A plethora of guidelines exist to guide healthcare professionals in the management of IDA in CKD:
- KDQOI (2006)
- UK Renal Association (2010)
- UK NICE Guideline 114 (2011)
- Kidney Disease Improving Global Outcomes - KDIGO (2012)
- CARI (2012)

Deciding which guidance to apply to practice can be a challenge whilst striving to provide the best level of care based on the highest level of available evidence. The majority of renal units will have protocols for anaemia management which will include the treatment of IDA in both the dialysis and non-dialysis population.

What does the evidence say?

KDIGO recommend iron supplementation be used when an increase in Hb concentration without starting ESA treatment is desired, based on patient symptoms, overall clinical goals, including transfusion avoidance, improvement of anaemia related symptoms and exclusion of active infection. The iron markers and parameters utilised by KDIGO are Serum Ferritin <500µg/L, %TSATS <30%.

KDIGO suggests a 1-3 month trial of oral iron therapy for adults not receiving haemodialysis if an increase in Hb is required without the use of ESA therapy and Serum ferritin <500µg/L, %TSATS <30%.

UK NICE Guidance recommend
- Investigating and managing anaemia in people with CKD Hb level <11 g/dl (111g/L) or <10.5 g/dl in those under 2 years and or/symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations are present
- Those receiving ESA therapy maintain serum ferritin levels between 200 and 500 µg/l in both haemodialysis and non-haemodialysis patients, %TSATS >20% (unless ferritin is >800 µg/l) or %HRC< 6%
- Those requiring correction of IDA maintain
  - Serum ferritin > 200 µg/l
  - %TSAT > 20% (unless ferritin > 800 µg/l)
  - %HRC < 6% (unless ferritin > 800 µg/l)

Review iron doses if serum ferritin rises above 500μg/L.

Whether to use oral or intravenous iron supplementation in those with CKD not receiving haemodialysis is a continuing debate and the evidence to date, does not support a clear preference or advantage for either. A trial of oral iron may be more practical for those with mild IDA and who need to avoid excess venepuncture. The main aim of treatment should be based on patient symptoms, and severity of IDA.

Studies such as the FIND Study are currently in progress to further investigate a direct comparison between oral and IV iron. It is hoped that the results of such studies will provide clear evidence to guide us in the optimal treatment and management of IDA.
Questions

1. What investigations are required to diagnose IDA?
2. What factors influence the tests used to identify IDA?
3. Which tests are used to diagnose IDA in CKD?
4. Which medicines are most effective in the treatment of IDA?
5. How can guidelines be used in practice to ensure all patients with CKD have access to treatment of IDA?

References