Introduction
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Chronic renal disease (CRD) has been defined as a pathophysiologic process with multiple etiologies, resulting in the inexorable attrition of nephron number and function and frequently leading to end stage renal disease (ESRD). ESRD represents a clinical state or condition in which there has been irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy in order to avoid life threatening uremia. The pathophysiologic process must last for more than 3 months in order to make the diagnosis of CRD.

CRD has been graded into five different stages, based on glomerular filtration rate –

**STAGES OF CHRONIC RENAL DISEASE:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min per 1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>At increased risk</td>
<td>90 (with risk factors)</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Renal failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>
HAEMATOLOGICAL DISORDERS IN CRD

The close relationship between haematopoiesis and the kidney was first recognized by Richard Bright in 1836 when he described the association between anemia and chronic renal failure (CRF).

A lot of progress has been made in this field since then, in order to understand the relationship between anemia and CRD and now it is well established that much of the morbidity in renal failure patients is because of the consequences of their chronic anemia. Disorders of white cell and platelet function have also been described in renal failure, but these are of secondary importance compared with those related to the red cell.

PATHOPHYSIOLOGY OF ANEMIA IN CKD

Anemia begins to develop as the GFR falls below 60ml/mt, and Hb typically falls below 11gm/dl as the GFR drops below 30ml/mt. Patients with diabetes and CKD tend to develop anemia earlier and to a greater degree than patients without diabetes.

FACTORS CONTRIBUTING TO DEVELOPMENT OF ANEMIA IN CKD

The major determinant of renal anemia is depressed erythropoiesis which is primarily due to relative erythropoietin (Epo) deficiency.

Various other factors that contribute to development of renal anemia include –

- Reduced red cell life span

- Iron deficiency
- Folate and B₁₂ deficiency

- Aluminium toxicity

- Marrow fibrosis resulting from hyper-parathyroidism

- Role of uremic inhibitors of erythropoiesis in development of renal anemia is still controversial and is under investigation.

Besides there are certain other factors that also play a role in development of renal anemia-

- Stress ulceration that can lead to substantial GI blood loss.

- Proton pump inhibitors, commonly prescribed in CKD to treat stress ulceration reduce iron absorption form GIT.

- Modified diets intended to reduce phosphate or protein in CKD also affect levels of dietary iron.

- Uremia leads to anorexia and nausea which further reduces intake and absorption of iron.

- Calcium binders also reduce iron absorption from gut.

- Blood loss due to hemodialysis

- Over zealous blood sampling

**TYPES OF ANEMIA IN CKD**

The peripheral blood film in a patient with CKD classically reveals a normocytic normochronic picture, occasionally with fragmented red cells or burr cells. The reticulocyte count is low for the degree of anemia and the white cell count is usually normal. There may be reduced, normal or
increased cellularity of bone marrow and the myeloid erythroid ratio may be decreased. There is a reduced red cell mass, but normal total blood volume except in patients who are fluid over loaded.

However, at times, the blood picture may be different from this typical presentation, being more in favour of microcytic hypochronic or macrocytic smear suggesting the predominant role of iron deficiency or B_{12}/Folate deficiency in causation of anemia, respectively.

**IRON DEFICIENCY IN CKD**

In developing countries like India, the commonest cause of iron deficiency, apart from increased requirement, are poor availability of iron in the predominant vegetarian diets and increased loses due to parasitic infestations (Park and Park). Mehta (1990) reported that dietary deficiency due to poverty, faulty food habits due to religious beliefs or other reasons, food fads and faulty cooking habits were the commonest factors contributing to iron deficiency and anemia. As the iron deficiency anemia is very wide spread in our country, it maybe a major contributory factor towards the anemia of CKD.

Besides, when the patients of CKD are put on erythropoietin (Epo) therapy, the rate of erythropoiesis is increased substantially, thus imposing significantly increased iron requirements. If the marrow stores are inadequate or the patients are not given iron concurrently, a state of functional iron deficiency in created leading to a picture of iron deficiency anemia. Therefore it is recommended that patient’s iron stores should be well repleted before starting Epo therapy and a maintenance dose of iron be continued during Epo therapy, keeping a watch on iron status of the patient.
ASSESSMENT OF IRON STATUS

There are four basic measurements that reflect the iron status of body. These are :-

- **Serum iron level** – Reflects the level of circulating iron

- **Serum ferritin level** – Reflects the stored iron in the reticuloendothelial cells of bone marrow, spleen and liver or in the parenchymal cells of the liver.

- **Percentage saturation of transferrin [TSAT]** – Transferrin is an iron binding protein in the blood which transports iron through the plasma and extravascular space. Normal saturation of transferring with iron is 30-50%.

- **Total iron binding capacity [TIBC]** – Reflects transferrin’s ability to bind iron. It represents the total amount of iron that can bind to transferrin to give 100% saturation of the binding sites.

TIBC is increased in iron deficiency and decreased in iron overload.

These are the best indicator of iron available for erythropoiesis and iron stores, but they do not provide absolute criteria for either iron deficiency or iron overload.
MANAGEMENT OF IRON DEFICIENCY IN CKD


NKF-K/DOQI provides certain guidelines for optimal management of iron deficiency in CKD patients:

- Assessment of iron status – Iron status should be assessed by serum ferritin and percent saturation of transferrin (TSAT).

- Target iron level

  - CKD patients should have sufficient iron to achieve and maintain a hemoglobin (Hb) of 11-12 gm/dl and a hematocrit (Hct) of 33% to 36%.

  - To achieve and maintain this target Hb/Hct, sufficient iron should be administered to maintain a TSAT of ≥20% and a serum ferritin level of ≥ 100ng/dl.

- Monitoring iron status

  - During initiation of Epo therapy and while increasing the Epo dose, in order to achieve an increase in Hb/Hct, the TSAT and the serum ferritin should be checked every month in patients not receiving I/V iron, and at least once every 3 months in patients receiving I/V iron, until target Hb/Hct is achieved.

  - Following attainment of the target Hb/Hct, TSAT and serum ferritin should be determined at least once every 3 months.
• Administration of supplemental iron

  • Supplemental iron should be administered to prevent iron deficiency and to maintain iron stores so that CKD patients can achieve and maintain a Hb of 11 to 12 gm/dl and Hct of 33 to 36 % in conjunction with Epo therapy.

  • If oral iron is given, it should be administered at a daily dose of at least 200mg of elemental iron for adults and 2 to 3 mg/dl for pediatric patients.

  • The adult CKD home hemodialysis and peritoneal dialysis patients may not be able to maintain adequate iron status with oral iron. These patients need to be put on I.V iron therapy.

  • A trial of iron is acceptable in the hemodialysis patients, but is unlikely to maintain TSAT ≥20%, se ferritin ≥100ng/ml and Hb/Hct at 11-12/33-36%.

  • To achieve and maintain a Hb of 11-12% and Hct of 33-36%, most hemodialysis patients will require I.V iron on a regular basis.

  • I/V iron can be administered on a variety of dosage schedule depending upon the iron requirement of the patient and the preparation used.

  • Most patients will achieve target Hb and Hct with TSAT and serum ferritin level <50% and <800ng/ml respectively. In patients in whom TSAT is ≥50% and/or serum ferritin is ≥800ng/ml, IV iron should be withheld for up to 3 months., at which time the iron parameters should be re-measured before I/V iron is
resumed. When TSAT and serum ferritin have fallen to >50% and <800 ng/dl respectively, I/V iron can be resumed weakly at a dose reduced by one third to one half.

- It is anticipated that once the target Hb/Hct levels and iron stores are achieved, the goal is to provide a weakly dose I/V iron that will allow the patient to maintain the target Hb/Hct at a safe stable iron level. The maintenance iron status should be monitored by measuring the TSAT and serum ferritin no less than every 3 months.

- Oral iron is not indicated for the CKD patients who requires maintenance doses of I/V iron.