

Iron Deficiency Anemia in Chronic Kidney Disease

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ABSTRACT

The total quantity of iron in normal adult body is about 4g. It is present as a component of hemoglobin and myoglobin. In Chronic Kidney Disease (CKD), the anemia that develops is frequently complex. The primary cause is inadequate production of erythropoietin by the diseased kidney. In patients undergoing dialysis, blood loss, which can also contribute to anemia, occurs due to blood retention in the dialysis and blood lines, frequent blood sampling, and vascular access complications. Patient with chronic kidney disease may have decreased dietary intake of iron that can contribute to the development of anemia.

KEY WORDS: Hemoglobin and myoglobin, Iron, Chronic kidney Disease, Ferritin.

Introduction

The total quantity of iron in normal adult is about 4g. It is present as a component of hemoglobin and myoglobin [1]. Iron binds different proteins either by its incorporation into a protoporphyrin ring. In the protoporphyrin ring iron may be incorporated as ferrous (Fe^{2+}) (or) ferric (Fe^{3+}) iron. The Fe^{2+} protoporphyrin complex is called heme while Fe^{3+} protoporphyrin complex is designated as hematin. Heme containing proteins include hemoglobin and myoglobin and certain

enzymes catalase and peroxidases. Non-heme proteins include ferritin, transferrin, several cytochromes and iron-sulfur proteins [2].

In the plant foods, iron is present in Fe^{3+} (Ferric) state, and is tightly bound to organic molecules. In the stomach where pH is low, Fe^{3+} dissociates and it is reduced to Fe^{2+} (Ferrous) by small compounds like ascorbic acid and amino acids like cysteine. Stomach also produces gastroferritin, a glycoprotein which combines with a small amount of ferric iron (Fe^{3+}). "Ferrous iron and gastroferritin" are easily absorbed into the mucosal cells of duodenum and jejunum by an unknown mechanism in the mucosal cells Fe^{2+} iron is also formed from dietary heme which is absorbed. In the mucosal cells, Fe^{2+} is oxidized to Fe^{3+} by ceruloplasmin, a copper containing protein. Ferrooxidase is another copper containing protein involved in this oxidation. In the mucosal cells Fe^{3+} combines with the intracellular carrier molecule, which is probably responsible for regulation of iron

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metabolism in the body [3]. Depending on the state of body iron metabolism, intracellular carrier molecule delivers iron to iron storage protein and plasma iron transport protein in proper proportions[4]. Under normal conditions, iron absorption depends on the body iron requirement. Only 10% dietary iron is absorbed because iron is nearly saturated. It transfers absorbed iron in proper proportions to iron storage protein and to iron transport protein present in plasma. In iron deficiency states, the iron is not saturated. So, more iron if available in the diet is absorbed. Under these conditions most of the iron absorbed is transferred to iron transport protein only. In an iron excess state, the intracellular carrier molecule is saturated. So, minimum iron is transferred to storage protein and transport protein [5]. Other factors like low phosphate diet increases iron absorption, where as high phosphate diet decreases iron absorption by forming insoluble iron phosphates. Phosphates and oxalates also decrease iron absorption. High or very low pH decreases iron absorption. Citrate promotes iron absorption [6].

From the mucosal cells, intracellular carrier molecule release Fe^{3+} into the plasma through an unknown mechanism, Fe^{3+} enter plasma from intestinal mucosal cells. Since free iron can generate free radicals in plasma, it combines with iron transport protein apotransferrin to form transferrin, which transport iron to storage sites. Apotransferrin combines with two molecules of Fe^{3+} to form transferrin [7]. Iron is mainly stored in the liver, spleen, bone marrow and intestine. In the intestine, apoferritin combines with Fe^{3+} , to form ferritin, which is an iron storage protein. In another tissue, transferrin is internalized by a receptor mediated process and iron is released. Then apoferritin combines with Fe^{3+} to form ferritin and it is stored [8]. Ferritin is continuously synthesized and degraded. The transfer of iron from ferritin to plasma apotransferrin involves

reduction of Fe^{+3} to Fe^{+2} , causing the releases of iron from ferritin. To facilitate its binding to apotransferrin, Fe^{+2} is oxidized rapidly. The reduction of Fe^{+3} to Fe^{+2} is catalyzed by ferritin reductase which requires two co-enzymes NAD and FAD where as oxidation is catalyzed by ceruloplasmin [9]. Iron over load is toxic, the excess of iron in the body results in its deposition as haemosiderin in various tissues, such as in the liver, spleen, skin and cardiac muscle. This turn also increase the risk of cardiovascular diseases. Iron over load leads to condition caused as haemochromatosis and haemosiderosis. Unabsorbed iron may generate free radicals and also it leads to oxidative stress. Deficiency of Iron occurs in three stages.

1. Iron storage depletion
2. Iron deficiency
3. Iron deficiency anemia.

In iron deficiency phase, iron stores are almost exhausted. Biochemically the serum ferritin is low, as well as the transferrin saturation. Hemoglobin concentration falls to the lowest limit of normal. Ultimately a hypochromic microcytic anemia sets [10].

Iron Deficiency Anemia in Chronic Kidney Disease (CKD)

In Chronic kidney (CKD), the anemia that develops is frequently complex. The primary cause is inadequate production of erythropoietin by the diseased kidney [11]. In patients undergoing dialysis, blood loss, which can also contribute to anemia, occurs due to blood retention in the dialysis and blood lines, frequent blood sampling, and vascular access complications. Patient with chronic kidney disease may have decreased dietary intake of iron that can contribute to the development of anemia [12]. This occurs when patients are encouraged to lower their intake of protein because of declining renal

function. Decreasing protein (Eg. meat) intake reduces iron intake and depletes iron stores. Absorption of iron from the gastrointestinal tract may also decrease [13]. Thus multiple factors can contribute to inadequate total body iron stores in patients with chronic kidney disease, the condition is known as “absolute iron deficiency”. Notably, one fifth of patients starting on dialysis have absolute iron deficiency [14]. This condition is commonly detected through clinical examination and laboratory tests. Measurement of serum ferritin and transferrin saturation (TSAT): A serum ferritin <100ug/ml and TSAT<20% indicate absolute iron deficiency [15].

Discussion and Conclusion

Iron status and Oxidative Stress

Iron is an essential element for mammalian cell growth. It is a required constituent of numerous enzymes, including iron-sulphur and heme proteins of the respiratory chain, as well as ribonucleotide reductase, which catalyses the rate-limiting step in DNA synthesis [16]. However, 'free' iron has the capacity to participate in oxygen free radical formation via Fenton chemistry [17]. Balancing the deleterious and beneficial effects of iron thus emerges as an essential aspect of cell survival. Ferritin plays a central role in the maintenance of this delicate intracellular iron balance [18]. This protein has the capacity to sequester up to 4500 atoms of iron in a ferrihydrite mineral core, and functions to store iron not required for immediate metabolic needs. Ferritin is a 24 subunit protein composed of two subunit types, termed H and L, which perform complementary functions in the protein. The H subunit is thought to play a role in the rapid detoxification of iron, it contains the majority of the ferroxidase activity that oxidizes iron to the (Fe+3) form for deposition within the core, whereas the L subunit facilitates iron nucleation, mineralization and long-term

iron storage [19]. Ferritin is highly conserved in evolution [20] and murine and human ferritin H subunits appear to play analogous roles [21]. Thus murine ferritin H, like human ferritin H, possesses a ferroxidase activity not found in human or mouse ferritin. These functions of ferritin suggest that it might serve as a cytoprotective protein [22], minimizing oxygen free radical formation by sequestering intracellular iron.

Several results support a role of ferritin as a protectant against oxygen free radical-mediated damage. Exposure of endothelial cells to heme was observed to induce ferritin synthesis and concordantly reduce the cytotoxic response of these cells to toxic doses of H₂O₂ [23]. A 6-fold induction of ferritin synthesis was observed in liver slices from rats treated with phorone, a glutathione-depleting drug that increases intracellular levels of reactive oxygen species (ROS)[24]. UV irradiation, which produces oxygen free radicals and damages DNA, has been shown to induce ferritin H mRNA [25], and ferritin protein [26]. Induction of ferritin may accompany oxidant stress and, by inference, protect against it. On the other hand observations that superoxide can mobilize iron from ferritin led to the suggestion that exposure to oxygen radicals may actually increase the pool of reactive (reduced) iron and exacerbate oxidant injury [27]. In addition, there are reports [28] that H₂O₂ activates iron regulatory protein (IRP)-1, possibly through direct disassembly of the 4Fe-4S cubane cluster [29], or by activating a signal transduction pathway [30]. Activated IRP-1 and IRP-2 are proteins that function in the regulation of ferritin and other iron responsive mRNA species (reviewed in), repressing ferritin synthesis at a translational level [31]. Thus activation of IRPs would reduce, not increase, synthesis of both ferritin H and L in response to oxidative stress. IRP was inactivated by superoxide anions and H₂O₂ in

a cell-free system [32]. Thus the relationship between oxidant stress and ferritin synthesis exhibits considerable complexity [33].

Patients with end-stage renal disease are at a markedly increased risk for cardiovascular complications compared with the general population. In addition to traditional cardiovascular risk factors such as diabetes mellitus, hypertension, hyperlipidaemia or cigarette smoking, a number of population specific factors are implicated such as anemia, hyperhomocysteinaemia, hyperphosphataemia and vascular calcification, as well as inflammation and oxidative stress. Iron overload has been suggested to increase the cardiovascular risk in the general population. Iron supplementation is a wide spread clinical practice in ESRD, especially in patients on maintenance haemodialysis. Iron may therefore contribute to cardiovascular complications through effects on low density lipoprotein oxidation and endothelial dysfunction. Although the effects on iron stores and iron therapy on cardiovascular risk are not well defined in hemodialysis patients the iron hypothesis deserves attention [34]. Serum ferritin is frequently used as a marker of iron stores in uremic patients several studies have shown that a low serum ferritin concentration is a reliable indicator of iron deficiency among ESRD patients. However, a high serum ferritin may not be an optimal indicator of increased iron stores among dialysis patients because it is an acute phase reactant and its increase in dialysis patients may be based on factors unrelated to iron stores such as inflammation and malignancy. Some recent studies have indicated a significant association between increased serum ferritin and malnutrition as well as resistance to recombinant human erythropoietin [35].

To conclude, the present article indicates a state of iron overload in the patients. However, the increase in serum ferritin does not seem to

be as a result of this iron overload and could be due to other non-iron related causes like the Malnutrition- inflammation complex. A larger prospective study is required to substantiate these findings so that preventive measures can be initiated at an early stage to decrease the morbidity and mortality in these patients.

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