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Lactoferrin: A Promising Molecule for the Treatment of Anemia of Chronic Kidney Disease

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ABSTRACT

Commonly available therapeutic approaches for treating anemia of chronic kidney disease include oral iron supplementation such as ferrous fumarate, intra venous iron administration and erythropoiesis stimulating agents including erythropoietin, darbepoetin alfa, etc. Nowadays ESAs are used widely to treat anemia of chronic kidney disease and several studies have found that if used inappropriately it can even lead to cardiovascular diseases. The harmful effect of free iron in human body includes microbial growth promotion and free radical-induced reactions which can further cause deterioration of patient condition. Iron overload can lead to organ multiple organ failure in kidney disease patients. The iron level in the body is one of the significant factor for the effectiveness of erythropoietin. A well maintained iron homeostasis is required in the kidney disease patients to observe an effective treatment for anemia in chronic kidney disease patients. Lactoferrin, an iron-binding glycoprotein has been studied widely for its effect on iron homeostasis, anti-microbial activity, etc. Its safety and efficacy over other oral iron supplements have been established from several studies. This review article aims to support the need for further studies for attaining more vast knowledge regarding the use of lactoferrin in the treatment of anemia of chronic kidney disease.

Key words: Anemia in chronic kidney disease, free iron, erythropoiesis stimulating agents (ESA), Lactoferrin, Glycoprotein, Iron homeostasis

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INTRODUCTION

Anemia is a condition characterized by a low level of hemoglobin in the blood which can be resulted from different underlying pathologies. As per the WHO definition, when hemoglobin levels fall from 13g/dL (in males) and 12g/dL (in females) it can be considered as anemia, however, some individuals are apparently normal even if the hemoglobin level is less than this. Since oxygen carrying capacity of blood is related to hemoglobin, it decreases corresponding to low hemoglobin level. From several forms of anemia iron deficiency anemia is one of the commonest, and its high prevalence in underdeveloped countries is mostly contributed by low iron intake through diet, multiple pregnancies, parasitic infestations, etc. [1]

Iron is an element highly essential for cell metabolism and growth, and is stored as ferritin and hemosiderin in the body (mostly in the liver). A major form of iron storage is ferritin. Iron forms complex with phosphate and hydroxide which is called as hemosiderin, when ferritin's capacity exceeds. In serum, iron is bound to the iron transport protein called apotransferrin and the bound form is called transferrin. The main laboratory markers indicating iron status in the body are serum ferritin and transferrin saturation. The treatment option for iron deficiency anemia is chosen based on the severity of the disease, which includes supplementation of iron and erythropoiesis- stimulating factor. [2]

CONVENTIONAL TREATMENTS

After thorough examination and diagnosis of the patient condition and severity of anemia, the treatment should be provided aiming to normalize the hemoglobin concentration, red cell indices, and to replenish iron stores. Further steps should be chosen if the provided treatment is not effective. Iron supplementation along with treatment of the underlying cause can correct anemia and replenish body stores of iron. Oral iron supplementation is the first choice of treatment. Easily available, cheap and most widely used oral iron supplementation is ferrous fumarate. The Ironpolymaltose complex is another most frequently used oral iron preparation. In situations like a failure of oral iron to produce any response, lack of compliance, and/or intolerance to oral iron, a switch to intravenous iron therapy is recommended to provide efficient management of the

condition. Iron III saccharate and iron carboxymaltose are most commonly used iv iron preparations. In severe cases, recombinant erythropoietin is suggested in addition to suitable iron preparation. [3, 4, 5]

LACTOFERRIN

Lactoferrin is a member of the transferrin family of iron-binding cationic glycoprotein, also called red protein. It has 300 times more affinity for iron compared to transferrin and the red color is due to this iron binding property. It is synthesized within the human body by exocrine glands and neutrophils. Colostrum of milk is detected to have the highest level of lactoferrin and small amounts are also detected in nasal fluids, pancreatic juice, tears, saliva, gastrointestinal secretions, and reproductive tissue secretions. During infection and inflammation, its biosynthesis is expected to be increased. [6]

From several studies regarding the functions of lactoferrin, it is found to be an emerging molecule with multiple functions in both physiological and pathological aspects, of which most important functions include its role in intestinal iron homeostasis, role of supporting host defence mechanism against microbial infection, role as an anti-inflammatory agent, protective role against cancer development and metastasis and as a regulator of morphogenesis etc. for executing each function, several distinct mechanisms are involved.

Pharmacokinetics and oral delivery of lactoferrin:

A thorough knowledge on pharmacokinetic behaviour and effective route of administration is required for appropriate therapeutic application of lactoferrin. Several animal studies are conducted widely for this purpose. A study of In *vivo* kinetics and lactoferrin distribution in rats shown the rapid clearance from plasma followed by iv administration, thus showing a dose dependent pattern of clearance and distribution and In *vivo* degradation was gradual.[7,8] Some studies indicated the internalization of lactoferrin by rat hepatocytes, but some shown its uptake by endothelial and kupffer cells.[9,10] In a study where lactoferrin was administered through iv and intraperitonial route shown a preferential binding to the endothelial cells in the body, and its considerable concentration in lymphatic system shows its implication in anti-microbial therapy.[11]

Since lactoferrin is a protein it can be degraded by the GI acids thus oral delivery of lactoferrin needs development of innovative technologies which should mainly focus on the stability maintenance and permeability to improve oral bioavailability. Chemical modification of lactoferrin with PEG showed increased GI stability and muco-adhesive chitosan shown to be with both enzyme inhibiting and absorption enhancing properties. Bioavailability of lactoferrin has been successfully enhanced by lipid based particulate carrier system. More effective and suitable oral drug delivery system should be developed through further research inorder to utilize the potential lactoferrin molecule.[12]

Lactoferrin in treatment of anemia of chronic kidney disease:

The total body iron content is distributed into functional and storage compartments. About 80% of the functional iron is found in hemoglobin; the rest is found in myoglobin and iron-containing enzymes. About 15% to 20% of total body iron is found in the storage pool which is represented by hemosiderin and ferritin. Iron is recycled within the body and is transported through the blood in bound form with transferrin, which is normally one third saturated with iron. This plasma transferrin delivers iron to cells and erythroid precursor for the synthesis of hemoglobin. In excess, free iron can be highly toxic and promote harmful processes such as microbial growth, free radical-induced cellular damage, etc. thus the iron should be in sequestered form for storage and iron homeostasis should be regulated thoroughly. Lactoferrin is thought to be involved in iron absorption from the intestine, although it has been a matter of debate over the years. [13,14]

High bioavailability of iron and its abundant concentration in breast milk supports the role of lactoferrin in intestinal iron absorption. In addition, lactoferrin is relatively stable in gastric acid and resistant to proteolysis. [15]

Several studies have shown the effectiveness of lactoferrin in the treatment of iron deficiency anemia. Natsue Koikawa et al. (2008) studied the preventive effect of lactoferrin intake on anemia in female long-distance runners and described the benefits of taking lactoferrin along with iron preparations. The ferritn, red blood cells count, and serum iron were significantly lower in group that only took iron suppliments, but there was no significant change in the group which were taking lactoferrin along with iron, thus inferred that lactoferirin can be useful in prevention of iron deficiency anemia.[16] Carmine Nappi et al. showed that bovine lactoferrin has the same efficacy in restoring iron deposits as ferrous sulphate in pregnant women with iron deficiency anemia with significantly fewer gastrointestinal side effects.[17] R. Paesano et al. (2010) described the efficacy of oral bovine lactoferrin in curing iron disorders in pregnant and non-pregnant women, and its effect on regulating iron homeostasis, also suggest the lactoferrin as an extremely valid natural drug, with few adverse effects, prevents and cures iron deficiency anemia more effectively than ferrous sulphate.[18] The same group conducted another study suggested that bovine lactoferrin represents a promising alternative to ferrous sulphate oral administration in treating iron deficiency anemia in pregnant women, with few adverse effects.[19] Rosalba Paesano et al. (2014) showed that lactoferrin is a significantly more effective option in curing iron deficiency anemia in pregnant women suffering from hereditary thrombophilia.[20,21] Mohamed Rezk et al. (2015) showed that lactoferrin helped to improve haemoglobin level than ferrous sulphate in treating iron deficiency anemia in pregnant women and it also states that a number of subjects in group receiving ferrous sulphate requested for a change of drug.[22,23]

The prevalence of Anemia of chronic disease is more in patients suffering from any infections, chronic kidney disease, autoimmune disease or cancer. Low serum iron and preserved marrow iron, and Iron deficiency anemia are characteristic features of anemia of chronic kidney disease. Hypoferremia, Interleukin-6(IL-6), and hepcidin are interrelated factors which mediate the pathologic changes leading to ACD. Hepcidin plays a major role in mediating interactions between the immune system and iron metabolism. It is produced by hepatocytes. This peptide hormone acts as a key regulator of iron transport through the membranes, controls intestinal iron absorption, mobilization of stored iron in hepatocytes, and also controls the iron recycling by macrophages. Ferroportin is an iron exporter seen on macrophage, hepatocytes, and enterocytes, and it is the only known iron exporter in these cells. Efflux of iron through this iron exporter is inhibited by hepcidin. During inflammation or infection increased level of IL-6 directly induces hepcidin synthesis which further leads to hypoferremia, thus for invading microorganisms, the plasma iron availability will be limited. However erythropoiesis

needs iron for hemoglobin synthesis, thus hypoferremia leads to Anemia associated with chronic disease. [24]

Iron therapy with or without concomitant administration of erythropoiesis-stimulating agents has been used in the management of anemia in chronic kidney disease population for many years. The Consideration for iron overload must be looked into, to prevent toxic and harmful effects of free iron. Oral administration of iron stimulates hepcidin synthesis which can lead to failure of iron supplements to cure ACD to an extent. In this respect, the novel and hopeful approach to treat ACD with lactoferrin in place of iron supplementation is of utmost importance. Lactoferrin chelates with two ferric ions per molecule, also down-regulation of inflammation reduces IL-6 production and independently reduce hepcidin gene expression thus helps to prevent hypoferrem+ia. From various studies in comparison to iron salts lactoferrin is found to have better compliance because of little or no gastrointestinal adverse effects which usually occur with normal iron supplements. [25,26,27]

CONCLUSION

Lactoferrin is a promising molecule with multiple functions including a role in maintaining iron homeostasis. It's safety and efficacy in preventing and treating iron disorders have been proven from various studies and further studies should be conducted in order to obtain more vast knowledge regarding the use of lactoferrin to establish the value of lactoferrin over other existing treatment options for anemia of chronic disease. Development and application of new innovative technologies to improve the oral bioavailability of lactoferrin is necessary in order to explore more unidentified uses of the molecule, and to improve the efficacy in already established therapeutic effects.

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