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ANALYSIS OF IRON METABOLISM AND CHELATION THERAPY IN HEMOSIDEROSIS

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Abstract:

Iron is an essential metal found in all living organisms including microbial, cancer and normal human cells. The main objective of the study is to analyse the iron metabolism and chelation therapy in hemosiderosis. This descriptive study was conducted in SIMS, Lahore during 2019 to 2020. This is basically a descriptive study. Hemosiderosis (iron overload) is another potential complication of transfusions. Iron is highly reactive and easily alternates between two states – iron III and iron II – in a process which results in the gain and loss of electrons, and the generation of harmful free radicals (atoms or molecules with unpaired electrons). It is concluded that nutritional iron overload requires years of supplementation to develop. Patients may take over the counterpreparations of iron supplements for a perceived health benefit and be unaware that it carries potential risks when taken for a long period of time.

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INTRODUCTION:

Iron is an essential metal found in all living organisms including microbial, cancer and normal human cells. More than a quarter of the human population is affected at some stages in their life by iron deficiency. Similarly, many millions suffer from other abnormalities of iron metabolism, such as iron overload in hereditary haemochromatosis which is caused by increased iron absorption and iron overload in thalassaemia which is a result of chronic transfusions [1]. Iron also plays an important catalytic role in free radical pathology and oxidative damage which is observed in almost all major iron loaded and non iron loaded diseases such as cardiovascular, neurodegenerative, hepatic and renal diseases, as well as in cancer and ageing [2].

Most of the diseases related to iron metabolic imbalance can be treated using established and effective therapeutic approaches, *e.g.*, iron supplementation for the treatment of iron deficiency anaemia and venesection in hereditary haemochromatosis. Iron overload in thalassaemia is more difficult to treat using chelation therapy and the same applies for the treatment of the anaemia of chronic disease in many conditions such as cancer, rheumatoid arthritis and haemodialysis, where oral or intravenous iron, with or without erythropoietin combination may be used [3].

Most of the therapies of abnormal iron metabolism described above are widely applied in developed countries but there are financial constrains for their use by patients in the developing countries [4]. In particular the treatment of thalassaemia using regular transfusions and chelation therapy and also the use of erythropoietin in the anaemia of chronic disease is not affordable for the vast majority of patients in the developing countries. However, despite the wide availability of the chelating drugs DF, L1 and deferasirox (DFRA) in developed countries and indications that the use of appropriate effective protocols can lead to the complete treatment of iron overload, their application to thalassaemia patients appears to be influenced by physician decisions associated with literature rivalry and commercial interests [5]. As a result of the commercial interference and influence which is mainly caused by the manufacturers of chelating drugs and their marketing methods the overall treatment outcome, safety and survival of the thalassaemia patients is greatly affected. Clinical trials and preclinical studies suggest that there are increasing prospects of using chelation and in particular L1 as a universal antioxidant in non-iron overload diseases such as neurodegenerative, cardiovascular, renal and infectious diseases as well as cancer and ageing [6].

Objectives:

The main objective of the study is to analyse the iron metabolism and chelation therapy in hemosiderosis.

MATERIAL AND METHODS:

This descriptive study was conducted in SIMS, Lahore during 2019 to 2020. This is basically a descriptive study. Hemosiderosis (iron overload) is another potential complication of transfusions. The incidence of iron overload typically increases with number of transfusions. The single major risk factor for TRIO was number of transfusions with a prevalence of greater than 35% in patients receiving over 10 transfusions. Four patients with TRIO and elevated liver function tests received chelation therapy.

Mechanisms of iron toxicity:

Iron is highly reactive and easily alternates between two states – iron III and iron II – in a process which results in the gain and loss of electrons, and the generation of harmful free radicals (atoms or molecules with unpaired electrons). These can damage lipid membranes, organelles and DNA, causing cell death and the generation of fibrosis. In health, iron is 'kept safe' by binding to molecules such as transferrin, but in iron overload their capacity to bind iron is exceeded both within cells and in the plasma compartment. The resulting 'free iron', either within cells or within plasma, damages many tissues in the body or is fatal unless treated by iron chelation therapy. Free iron also increases the risk of infections [7].

Distribution and consequences of transfusional iron overload:

In the absence of iron overload, uptake of iron into cells is controlled by the interaction of transferrin with its receptors - mainly on red cell precursors, hepatocytes and dividing cells. In iron overload, transferrin becomes saturated and iron species that are not bound to transferrin are present in plasma (plasma non transferrin bound iron, or NTBI). The distribution of NTBI uptake is fundamentally different from transferrin uptake, and is thought to involve calcium channels [8]. Organ damage in transfusional iron overload reflects the pattern of tissue iron uptake from NTBI. Some tissue are spared from iron loading through this mechanism (such as skeletal muscle), while other such myocardial muscle, endocrine tissue and hepatocytes take up NTBI rapidly. This iron is then stored as ferritin or haemosiderin which are visible by MRI. The myocardial iron overload induces

heart failure from cardiomyopathy in patients without chelation in as early as the second decade of life. Iron overload also causes pituitary damage, leading to hypogonadism, growth retardation and delayed puberty. Endocrine complications, namely diabetes, hypothyroidism and hypoparathyroidism are also seen [9].

Sources of chelatable iron:

Only a very small fraction of body iron is available for iron chelation at any moment of time. This is because iron chelators interact with low molecular weight 'labile' iron pools better than with iron stored as ferritin or haemosiderin. Labile iron is constantly being generated, so that the efficiency of chelation is better when a chelator is available at all times (chelator present 24 hours a day). 24h chelation also has the potential to remove toxic labile iron pools within cells continuously, which is particularly important in reversing heart failure. Chelatable iron is derived from two major sources: iron derived from the breakdown of red cells in macrophages (about 20 mg/day in healthy adults), and iron derived from the catabolism of stored ferritin iron within cells [10]. Most of the storage iron in the body is in hepatocytes, and the ferritin in these cells is turned over less frequently (every few days). Iron chelated within the liver is excreted though the biliary system, or circulates back into plasma and is excreted in the urine. The extent to which this chelated iron is eliminated in faeces or urine varies with each chelator.

DISCUSSION:

Iron is a micronutrient which if deficient or excessive may cause morbidity and mortality. In 1889, Von Reclinghasen observed the association of iron accumulation in the pancreas and the development of diabetes due to its associated tissue injury. Knowledge about hemochromatosis has grown dramatically from the era when Von Reclinghasen made his observations to the current understanding of iron homeostasis [1, 2].

The availability of molecular genotyping of the HFE gene highlights the paradox of a common mutation but a rare disease. The prevalence of detectable mutations in North America is between 1 in 200 and 1 in 500 and is even more common in some northern European countries. They are transmitted, with rare exceptions, in an autosomal recessive pattern. Most people with mutations never develop the disease. Likewise, a significant number of patients with the clinical phenotype of primary hemochromatosis have no detectable HFE mutation [3].

The liver is the conductor of systemic iron balance, sensing a variety of iron related signals and modulating iron absorption and storage by hepcidin expression [4]. The relationship of serum ferritin and total body iron stores has been clearly established. As the ferritin increases, the risk of significant liver disease rises [5]. It may be elevated in the absence of iron overload, however, and competing comorbidities such as alcoholic liver disease, hepatic steatosis, or viral infections may confuse the diagnosis because of the clinical similarities.

The diagnosis of iron overload is often overlooked because the signs and symptoms are commonly associated with other diseases, such as chronic fatigue, cirrhosis, diabetes, congestive heart failure, hypogonadism, osteoporosis, and arthritis. In the absence of acute or chronic inflammation, screening for iron overload is warranted upon discovery of ferritin levels above 200 ng/mL and transferrin saturation above 45% in women or ferritin more than 300 ng/mL and transferrin saturation greater than 50% in men. Specialized MRI scanning of the liver provides indirect evidence of iron overload. Liver biopsy provides a direct measurement of liver iron concentration along with the pathologist's assessment of liver histology [6].

A wide array of treatment strategies exploiting the role of hepcidin in the regulation of iron homeostasis are under development [7]. Currently, however, the treatment of hemochromatosis whether genetic or acquired is serial phlebotomies continuing until the ferritin is less than 50 ng/mL and iron saturation is less than 50%. Those patients with genetic hyperabsorption of iron will require periodic phlebotomies indefinitely to maintain their iron stores at a safe level. As in our patient, iron overload due to chronic ingestion of iron in the absence of mutations that upregulate iron absorption should not require phlebotomies after reaching acceptable levels of ferritin and iron saturation [11].

CONCLUSION:

It is concluded that nutritional iron overload requires years of supplementation to develop. Patients may take over the counter preparations of iron supplements for a perceived health benefit and be unaware that it carries potential risks when taken for a long period of time. Medical professionals of all specialties should query their patients as to whether they take supplements with iron and discontinue it if there is no medical indication.

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