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Clinical Usefulness of Ferritin in Health and Diseases

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Abstract: **Ferritin is the storage form of iron and its role has been implicated in s variety of human diseases. Among the assays carried out to assess the role of iron, such as serum free iron, protein bound iron, transferrin and % saturation, the plasma content of ferritin is the most clinically useful parameter to understand its role in many diseases such as obesity, DM, anemia and diseases associated with liver, kidney, cardiac, reproductive and psychiatric disorders. This review article brings out the outcome of research done on the clinical usefulness of ferritin in the diseases outlined above. The content of this review article will be useful to undertake iron supplement as curative therapy for patients with hypo ferritinemia.**

Keywords**: Ferritin, DM, Anemia, Obesity, Infertility, Psychiatry.**

1. INTRODUCTION

Ferritin is the major storage form of iron in the human body and its circulating level in plasma is directly linked to many diseases and its role has been extensively studied. Plasma levels of ferritin are linked to many diseases. The aim of this review article is to bring out the research findings done during the last 2 decades on the clinical usefulness of ferritin in a variety of disorders.

2. FERRITIN AND DIABETES MELLITUS

Emerging evidence suggests that a strong link may exists between elevated baseline body iron stores and high risk of incident Type 2 Diabetes Mellitus (T2DM) in general populations, but the precise magnitude of the associations remains uncertain. Elevated levels of Serum Ferritin (SeF) may help identify individuals at high risk of T2DM. Further research is warranted to establish causality of these associations and to ascertain which patients are likely to benefit from lifestyle or therapeutic interventions [1]. An elevated SeF concentration recently has been shown to be associated with Coronary Artery Disease (CAD) and its risk factors, including blood glucose concentration. T1DM is a condition frequently associated with elevated levels of SeF. Treatment with deferoxamine intramuscularly was not effective in improving control of glucose in some patients with T2DM [2]. Women in the highest quintile of SeF had a two fold increased risk of developing Gestational Diabetes Mellitus (GDM) adjusted for several known risk factors. Similar results were obtained with a nested case-control study, in which women in the highest tertile of SeF had a greater than two fold increased risk of GDM. However, these effects were modified and became nonstatistically significant after additional adjustment for prepregnant Body Mass Index (BMI). The association, at least in part, is mediated by the maternal fat mass and obesity, and hence a link may exist between elevated SeF and low-grade inflammation [3].

There is a link between T2DM, Insulin Resistance (IR), glycemic control, diabetic complications and hyper ferritinemia. Although some studies suggest that SeF concentration is positively correlated with IR and with the risk of acquiring T2DM, substantial iron overload is not a typical feature of DM. There is no correlation between SeF level and glycemic control or diabetic micro angiopathic complications [4]. SeF was increased in diabetic patients as long as glycemic control

is not achieved. There was also a correlation between SeF level and diabetic retinopathy. An independent positive association exists between SeF and markers of glucose homeostasis [5].

Transient hyperferritinemia is a feature of newly diagnosed DM but not of established DM with poor control. If used to screen diabetic patients for haemochromatosis, SeF should be measured in established DM rather than at diagnosis [6]. It is suggested that an excessive absorption and storage of dietary iron might contribute in the pathogenesis of T2DM and its complications. Serum iron or SeF levels did not differ significantly and there was no correlation between HbA1c level and serum iron or SeF levels between diabetic patients' groups, suggesting that iron does not have a major role in the development of DM or diabetic retinopathy [7].

Gamma Glutamyl Transaminase (GGT) and SeF were correlated with each other, and had synergetic effect on the risk of T2DM in women and the mechanism involved might be enhanced Oxidative Stress (OS) [8]. There was a positive correlation between SeF and Fasting Plasma Glucose (FPG) and HbA1c. There was no correlation between SeF and age, sex, Metabolic Syndrome (MetS), coexistent hypertension, total cholesterol, Low Density Lipoprotein Cholesterol (LDL-C) and triglycerides (TGL) [9]. For both men and women, the highest prevalence of Metabolic Syndrome (MetS) occurred in the highest quartile of SeF. The odds ratios increased progressively across the ferritin quartiles. Increased SeF concentrations are associated with the MetS among men and women in China [10]. Exposure to several gonadotoxins, transfusional iron overload and nonmyeloablative conditioning with radiation causes severe testicular atrophy leading to extensive damage to seminiferous tubules and possibly Leydig cells and gonadotropins were efficacious in restoring the reproductive capability [11].

3. FERRITIN AND OBESITY

Serum Alanine Transferase (ALT) was positively correlated to IR. Using a multivariate model, with the android/gynoid fat mass ratio as an additional independent variable, SeF remained correlated with serum Aspartate Transferase (AST) and ALT. Abnormal serum aminotransferase values are uncommon in severely obese children in France. Android fat mass distribution, IR and higher SeF concentrations are significantly associated with liver abnormalities [12]. Growing evidence has shown that SeF concentrations are associated with obesity and IR and non-alcoholic fatty liver disease. In obesity, SeF, putatively entailing increased iron storage, is independently associated with lipid derangements and transferase levels, and the association with the latter persists after weight changes [13]. The association between SeF as well as Hemoglobin (Hb) level and individual MetS components is unclear. Erythropoietin (EPO) levels in subjects with MetS have not been determined previously. Subjects with MetS have elevated Hb, SeF, erythropoietin and haptoglobin concentrations. Higher Hb levels are related to all components of MetS. Higher SeF levels associate with TGL, abdominal obesity, elevated glucose or low HDL-C. Haptoglobin levels associate with blood pressure or elevated glucose. However, erythropoietin levels are related only with abdominal obesity. Higher serum EPO concentrations may suggest underlying adipose tissue hypoxemia in MetS [14]. SeF concentration was found to be related with dyslipidemia, hypertension and abdominal adiposity. The correlation between whole body iron storage and the components of MetS was reported in several studies previously. SeF is also known to be a marker of inflammation and increases in Cardio Vascular Disease (CVD). Correlation between increment of SeF concentrations and metabolite risk markers regards of cardiovascular risk may exist and hence could be a risk marker for atherosclerotic disease [15].

SeF levels were significantly higher in obese women with MetS in comparison with obese women without MetS. No differences in the other markers of iron status were observed. Diabetic patients had higher ferritin levels than non-diabetic patients. Among the components of MetS only diabetes was independently associated with SeF levels in normal and in patients with MetS. MetS and in particular T2DM is the main contributor to the high ferritin levels reported in obesity [16]. Weight to Hip Ratio (WHR) showed significant positive associations with log SeF concentration independent of age and BMI. The association was strongest at age 20-29 y among those with BMI below the median. SeF concentration is associated with WHR and other indices of body fat distribution and obesity [17].

Both severe obesity and abdominal obesity based on WHR showed consistent longitudinal associations. Elevated SeF levels may have been a predictive factor for obesity [18]. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance observed in women with elevated SeF levels. Elevated SeF levels are associated with increased IR and risk of diabetes in obese women but not in non-obese women. However, higher SeF levels were correlated with a greater risk of hyperglyceridemia in both obese and non-obese women. Therefore, hypertriglyceridemia in women with

Poly Cystic Ovarian Syndrome (PCOS) might be associated with iron metabolism [19]. In male, SeF levels showed positive association with obesity, and it appears to be associated with obesity in Korean male adolescents [20].

4. FERRITIN AND ANAEMIA

Iron deficiency is the single most prevalent nutritional deficiency worldwide. It accounts for 5% of anemia in American women and 2% of American men. Intravenous iron supplementation fell out of favor secondary to the presence of infrequent but serious side effects. Newer and safer intravenous iron preparations are now available but are currently underutilized. Standard treatment for iron deficiency anemia in adults does not cause a rise in SeF until Hb levels are normal. The early rise seen with double dose is most likely due to absorption of iron in excess of utilization for erythropoiesis resulting in temporary storage. When iron is discontinued, stores are rapidly depleted as reflected by the prompt decrease in SeF [21].

Elevated serum and tissue SeF are linked to CAD, malignancy and poor outcomes following stem cell transplantation. SeF is directly implicated in less common but potentially devastating human diseases including sideroblastic anemias, neurodegenerative disorders and hemophagocytic syndrome. Additionally, recent research describes novel functions of SeF independent of iron storage [22]. The determination of SeF is of particular relevance as a significant correlation was ascertained between low SeF levels and the incidence of preterm labor: 52.3% of the women with SeF levels below 10 ug/L and only 9.5% of the women with levels above 20 ug/L went into preterm labor. A convincing explanation for this has not yet been found [23]. Prenatal patients with anemia, only approximately half had an iron deficiency. Diagnostic and therapeutic approaches to screening for anemia in pregnancy should be reconsidered and further evaluated [24].

SeF is the most powerful non-invasive test for the diagnosis of iron deficiency anaemia in patients with liver cirrhosis and it should be the primary test of choice in patients suspected of having the disease. When the level is less than 50 ug/L, iron supplement may be prescribed without necessitating bone marrow aspiration [25]. In the absence of response to oral iron, or if the anemia is severe or clinical suspicion of important disease persists, one must insist on diagnostic evaluation. Repeat endoscopic studies should be considered in many cases and if both still show normal results, investigating the small bowel must be considered. The main techniques in this case are capsule endoscopy, followed by enteroscopy [26]. Trends of the commonly obtained red cell indices, mean corpuscular volume, and the red cell distribution width can provide valuable diagnostic information. Once the diagnosis is established, upper and lower gastrointestinal endoscopy is usually indicated. Nevertheless, in many cases a gastrointestinal source is not found after routine evaluation. Additional studies, including repeat upper and lower endoscopy and often investigation of the small intestine may thus be required. Although oral iron is inexpensive and usually effective, there are many gastrointestinal conditions that warrant treatment of iron deficiency with intravenous iron [27]. It is also important that SeF was the only one of these measurements which was able to differentiate between iron deficiency, and anemia due to infection. Patients with anemia due to infection had elevated SeF levels. In 17% of patients no reason for the fall of Hb could be shown and a plausible explanation for the low level is extensive hemodilution [28].

5. FERRITIN AND LIVER DISEASES

No correlation was found between SeF or serum transferrin (sTfR) and serum iron. Neither was any correlation observed between the magnitude of the changes in SeF and the changes in serum iron, sTfR or circulating platelets or reticulocytes observed in the serially followed alcoholics. These observations indicate that elevated SeF in alcoholics is associated with the degree of liver affected and not with the degree of EPO activity [29]. In patients with liver cell damage, the SeF iron saturation in serum was significantly higher than that found in groups with iron overload disease, probably indicating the release of intracellular iron-rich SeF into the blood. The monitoring of patients undergoing bone marrow transplantation indicated that the release of iron-rich and iron-poor SeF occurred during phases of hepatocellular damage and inflammation, respectively, indicating the benefits of SeF iron measurement to be marginal in patients with iron overload disease [30].

SeF is more frequently elevated in abusing patients with alcoholic liver disease than in patients with other chronic liver diseases such as autoimmune liver diseases and hepatitis C. Because SeF decreases rapidly during abstinence, the measurement of SeF for the detection of haemochromatosis in patients abusing alcohol should be postponed until the patients are abstaining. Most of the patients with increased SeF have normal STfR values which can be used to separate them from haemochromatosis [31]. Men were more likely to have elevated SeF levels than women and were at higher risk of developing Primary Hepatocellular Carcinoma (PHC). Men who were chronically infected with HBV and had SeF

above 300 ng/mL had a 50% chance of developing PHC during the follow-up period, compared with a 20% risk of PHC for men with lower SeF levels. This elevated risk of PHC in men with elevated SeF levels was confined to the first 3 years of follow-up [32]. An extremely close correlation was found between SeF and an empirical index derived from the product of the serum transaminase times liver iron concentration, implying that the circulating level depended on both the degree of hepatocellular injury and liver iron store. There was a close linear correlation between the SeF -transaminase ratio and liver iron concentration in all disorders studied, and this index may prove to be the most useful value for diagnostic purposes [33].

6. FERRITIN AND KIDNEY DISEASES

There was a moderately negative correlation between serum iron and erythrocyte ferritin levels. Erythrocyte ferritin levels may be useful in complex diagnostic assessment of the anemic syndrome in Chronic Renal Failure (CRF) patients and is a reliable indicator of iron overload in hemodialysis patients. It gives no advantage in the evaluation of iron metabolism of medically treated CRF patients [34]. SeF levels in patients with Acute Renal Failure (ARF) were also higher than the corresponding levels of normal controls, but did not differ significantly from those measured in patients with acute infection and SeF levels are increased in ARF patients and do not reflect serum iron levels [35]. Single SeF values should not be used to guide clinical decisions regarding treatment of chronic hemodialysis patients with intravenous iron due to significant analytical and intra individual variability [36].

In Maintenance hemodialysis patients, ferritin values above 500ug/L, especially in paradoxical conjunction with low iron saturation in hemodialysis patients are associated with inflammation. Strategies to dissociate inflammation from iron metabolism to mitigate the confounding impact of inflammation on iron and to improve iron treatment responsiveness may improve anemia management in Chronic Kidney Disease (CKD) [37]. Increased hepcidin across the spectrum of CKD may contribute to abnormal iron regulation and erythropoiesis and may be a novel biomarker of iron status and EPO resistance [38]. No significant association was found between the mean level of sTfR in CKD patients with the controls. sTfR had no statistically significant correlation with the levels of Hb, iron, ferritin and TIBC suggesting that owing to complexity of iron metabolism in CKD, sTfR cannot be used as a reliable marker of iron deficiency anemia [39].

7. FERRITIN AND CARDIAC DISEASES

There were no statistically significant associations between SeF and any of the cardiovascular end points for any of the groups. There was an apparent but non-significant u-shaped association between SeF and all causes mortality in black men and between SeF and CVD death in white women. However, in both cases very wide confidence limits preclude further interpretation. Overall, the results do not support the hypothesis that positive body iron stores, as measured by SeF, are associated with an increased risk of CVD, CHD or MI death or between SeF and all causes of mortality [40]. When other risk factors of CVD were included in the model, SeF level $\geq$ 200 ug/L was associated with CAD. High iron store, as assessed by SeF, was associated with the increased risk of CAD. Furthermore, it was a strong and independent risk factor in the incident of atherosclerosis in the Iranian male population [41].

After adjustment for the other variables, WHR was the only independent predictor of SeF and SeF levels in young men and women are associated with obesity, TGL and HDL-C in men and inflammation in women. Confounding may contribute to reports of associations between SeF and CVD [42]. SeF was positively associated with total cholesterol, TGL, systolic and diastolic blood pressures, BMI and Hb. No linear association was found between SeF and Ischemic Heart Disease (IHD) risk in men or in women, supporting a major role of iron status in the development of IHD in a healthy general population [43].

There is no evidence supporting the hypothesis that serum iron may be associated with CVD. Despite large number of studies published to date, the role of iron in CVD still generates a fair amount of debate, due to a marked disparity in results [44]. There was no association between SeF and physical activity, serum total cholesterol or serum HDL-C. In women aged 40-60 years, significant positive associations were found between SeF and the following risk factors: BMI, alcohol intake and TGL. There was no association between SeF and physical activity, tobacco smoking, total cholesterol, HDL-C or blood pressure. Associations were found between SeF and some risk factors for IHD in men and women. The clinical significance of these findings remains to be clarified. One may hypothesize that the 'missing link' between SeF and IHD in men is the relationship between SeF, TGL and blood pressure [45].

8. FERRITIN AND PCOS

No significant association was found in PCOS between SeF and C-Reactive Protein (CRP), HOMA-IR, BMI and WHR. Further no significant correlation observed between CRP and HOMA-IR as well as to BMI. The effect of metformin on reduction of SeF was not significant just in obese group and was not associated with metabolic and anthropometric indexes [46]. Increased SeF levels and iron stores may be involved in the development of abnormal glucose tolerance in women presenting with obesity and/or PCOS. Androgen excess (partly because of hyper androgenemia and partly because of menstrual dysfunction), IR, abnormal glucose tolerance, and the *HFE* His63Asp variant correlate with SeF levels in premenopausal women [47]. OS further increases the CVD risk in these women. Correcting OS with antioxidants along with monitoring the antioxidant status using a simple assay like ferric reducing ability of plasma could have a beneficial effect on OS induced IR and hyperandrogenism seen in PCOS women [48]. IR and hyperinsulinism and not the reduced menstrual losses secondary to from oligo- or amenorrhea, are responsible of the increased SeF levels and body iron stores found in overweight and obese women with PCOS [49].

SeF correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, TGL and total cholesterol in both obese and non-obese women. Obese women with high SeF levels exhibited higher IR, impaired glucose tolerance and liver enzymes than obese women with low SeF levels. However, among non-obese women, IR and risk of diabetes were not significantly different between the high and low SeF groups. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance observed in women with elevated SeF levels [50].

9. FERRITIN AND INFERTILITY

Endocrine complications due to haemosiderosis are present in a significant number of patients with beta-thalassemia major (BTM) worldwide and often become barriers in their desire for parenthood. The gonadal function of BTM patients is usually intact and fertility is usually retrievable. Meanwhile, a significant pro-oxidants/antioxidants imbalance with subsequent increased OS exists in patients with BTM, which is mainly caused by tissue injury due to overproduction of free radicals by secondary iron overload, but also due to alteration in serum trace elements and antioxidant enzymes [51]. The increased level of redox activity found in the follicular fluid from patients with BTM focuses the attention on the small fraction of redox-active iron ions as mediators of free radical production, inducing tissue injury and possibly contributing to impairment of reproduction in these patients [52]. High SeF were also significantly associated with Low Birth Weight (LBW). The risks of LBW and fetal growth restriction were significantly greater among women with moderate anemia compared with non-anemic controls. sTfR and low SeF were not associated with adverse birth outcome, but elevated SeF, which could be a marker of inflammation, was associated with increased risk of LBW. Preconception anemia, particularly iron-deficiency anemia, was associated with reduced infant growth and increased risk of adverse pregnancy outcome in Chinese women [53].

10. FERRITIN AND NEUROPSYCHIATRY

Patients with porphyria had inappropriately low EPO levels for the degree of anaemia compared to iron-deficiency patients although there was still a significant increase in EPO with decreasing Hb levels. In contrast, diabetic autonomic neuropathy patients demonstrated a significant decrease in EPO with decreasing Hb levels. Patients with acute porphyria may have inappropriately low levels of EPO. In contrast to the diabetic patients, this does not appear to be due to autonomic neuropathy but it may reflect mild renal tubular impairment [54]. The lower peripheral ferritin and iron levels in persons with Tourette's syndrome are consistent with findings in other movement disorders and suggest that lower iron availability may have a causal role in the pathophysiology of tic disorders. Lower iron stores may contribute to hypoplasia of the caudate and putamen, increasing vulnerability to developing tics or to having more severe tics. Lower iron stores may also contribute to smaller cortical volumes and consequently to reduced inhibitory control of tics [55].

The prediction of amphetamine optimal dose by SeF concentration suggests that iron supplementation should be investigated as a potential intervention to optimize response to psychostimulants at a lower dose in individuals with low iron stores and Attention Deficient Hyperactivity Disorder (ADHD) [56]. Zinc, SeF and magnesium levels were significantly lower in children with ADHD than controls, while copper levels were not significantly different. Children with inattentive type had significant lower levels of zinc and SeF than controls with no significant difference between them as regards magnesium and copper levels. Children with hyperactive type had significant lower levels of zinc, SeF

and magnesium than controls with no significant difference between them as regards copper levels. Children with combined type had significant lower levels of zinc and magnesium than controls with no significant difference between them as regards SeF and copper levels. Children with ADHD had lower levels of zinc, SeF and magnesium than healthy children but had normal copper levels [57].

SeF was strongly associated with CSF apolipoprotein E levels and increases due to Alzheimer's risk allele, *APOE-ε4*. These findings reveal that elevated brain iron adversely impacts on Alzhemier Disease (AD) progression, and introduce brain iron elevation as a possible mechanism for *APOE-ε4* being the major genetic risk factor for AD [58]. In multivariate analyses, levels of SeF ≥130.15µg/L were independently associated with PSD at two months after adjusting for all possible variables. Elevated SeF levels at admission are associated with Post Stroke Depression (PSD) and may predict its development at 2 months post-stroke [59]. Diabetic autonomic neuropathy patients demonstrated a significant decrease in EPO with decreasing Hb levels. Patients with acute porphyria may have inappropriately low levels of EPO. In contrast to the diabetic patients, this does not appear to be due to autonomic neuropathy but it may reflect mild renal tubular impairment [60].

11. CONCLUSIONS

This review article has brought out a brief outline about the clinical usefulness of serum ferritin assay in understanding its role in various types of common diseases linked to DM, Kidney, Liver, Cardiac, reproductive and psychaiatric disorders. Further, the content of this article will help future researchers to undertake more studies to evaluate the clinical usefulness of ferritin in a variety of disorders and to design supplementation studies for the benefit of patients.

Conflict of Interest: None

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