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A MINI-REVIEW OF SERUM FERRITINS IN DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is a vast worldwide public health problem affecting millions of people. This endocrine condition is the most common one. The disorder brings on significant morbidity, mortality, and chronic issues. Consistent hyperglycemia and alterations in protein, lipid, and carbohydrate metabolism due to absolute or relative insulin secretion or action deficits characterize this group of metabolic diseases with varying etiologies. The kidneys, eyes, nerves, heart, and blood arteries are especially vulnerable to the long-term damage or malfunction resulting from diabetes mellitus.

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1. INTRODUCTION

The majority of diabetic sufferers worldwide reside in India. The dubious title "diabetes capital of the world" also applies to India. From 2000 to 2030, the overall prevalence of diabetes was projected to rise from 2.8% to 4.4%. This number is expected to rise to 366 million by 2030, from 171 million in 2000, when diabetes was first estimated. According to projections, there will be 79.4 million diabetics in India by 2030, up from 31.7 million in 2000 [1-3]. The majority of people with diabetes have type 2 diabetes mellitus. From primarily insulin resistance with relative insulin shortage to primarily secretory defect with insulin resistance, Type 2 diabetes mellitus can present in several ways. A hormone is known as anabolic insulin [4]. It is a protein that the pancreatic islets of Langerhans beta cells make and secrete. Insulin works by attaching to a receptor on the target cells' plasma membrane. Insulin binding induces the receptor to dimerize [5, 6]. The signal is then broadcast once it has been internally processed. In reaction to hyperglycemia, insulin is secreted, increasing glucose uptake and using glucose by tissues to bring blood sugar levels back to normal. Protein synthesis, lipogenesis, anti-lipolysis and anti-ketogenic effects are all boosted by insulin [7].

Researchers have shown a correlation between high amounts of iron in the body and Type 2 and gestational diabetes. It has been shown that insulin sensitivity and the existence of insulin resistance syndrome are positively correlated with an increase in serum ferritin (SF). Normal adult haemoglobin covalently linked to a glucose molecule is glycated haemoglobin [8-10]. People with diabetes mellitus can effectively monitor their long-term glucose control using glycated haemoglobin. It gives a retrospective index of the averaged plasma

glucose values over a long period and is not affected by the significant swings seen when measuring blood glucose concentrations. Therefore, gyrated haemoglobin concentrations are important and frequently used as a supplement to blood glucose measurement for tracking long-term glycaemic management [11]. Glycated haemoglobin also serves as a gauge for the likelihood that diabetes complications would manifest. 3 to 5 g of total body iron is found in the liver, bone marrow, muscles, and 75% of that amount is found in the blood. All cells contain iron to some degree. Haemoglobin makes up about 75% of the total iron, followed by myoglobin at 5% and ferritin at 15%. For an adult Indian, iron intake is 20 mg, of which 1 to 2 mg are absorbed [12].

Iron is stored by the ubiquitous intracellular protein ferritin, which releases it gradually over time. It serves as a buffer against both iron overload and iron shortage. About 4000 ferric ions can be stored in a ferritin complex [13]. The presence of iron is a significant catalyst for ferritin synthesis. Male reference values for serum ferritin are 30-300 ng/mL, and female reference ranges are 10-160 ng/mL. Serum ferritin has been demonstrated to be a significant and independent predictor of the onset of diabetes mellitus in numerous prospective epidemiological investigations [14]. Overexposure to ferritin has been linked to an increased risk of diabetic Mellitus, coronary heart disease, and insulin resistance, prompting increased public attention to this topic. Serum ferritin is an example of an acute phase reactant [15].

2. SERUM FERRITTIN: BASIC BIOLOGY

Serum ferritin is an example of a protein in the body involved in the acute phase reaction. Even though nuclear localization and roles of ferritin have been speculated, and a mitochondrial form of ferritin has recently been revealed, ferritin is predominantly present in the cytoplasm of most tissues [16]. Ferritin has been the topic of recent in-depth reviews and is crucial for storing intracellular iron. Twenty-four individual proteins comprise ferritin, divided into the H and L subunits. Electrophoretic migration of the H subunit, the heavier of the two subunits, or the first isolation of isoforms from human heart tissue may be denoted by the letter H [17]. L stands for ferritin, lighter subunit-rich ferritin isolated from the human liver. Depending on the kind of tissue and stage of development, different ratios of H to L subunits make up the formed ferritin protein [18]. Separate genes on chromosomes llq and 19q encode human ferritin's H and L subunits. Additionally, both Hand L ferritin has many pseudogenes. Between ferritin H and L subunits in mammals, there is roughly 50% amino acid sequence homology; however, there is considerably more sequence conservation amongst subunit types (between mammalian H subunits, there is about 90% homology; among L subunits, there is about 80% homology) [19].

The iron content of serum ferritin is not very high. Serum ferritin may be glycosylated based on its capacity to bind concanavalin A [20]. According to immunological cross-reactivity with anti-ferritin L antibodies, it largely consists of the L subunit type. Uncertainties exist regarding serum ferritin's origin and precise secretory mechanism. It has been demonstrated that Kupffer cells, macrophages, and hepatocytes have secreted ferritin [21-23]. Serial ferritin L and tissue ferritin L are encoded by the same gene, despite a typical secretary signal on ferritin L. As a result, ferritin L was secreted from hepatocytes that had been transfected with the ferritin L cDNA through a conventional secretory pathway. But because there isn't a signal peptide sequence that triggers ferritin secretion, more research is needed to characterize the methods by which ferritin enters the secretory system. Iron, as well as the cytokines interleukin-1 (IL-1) and tumour necrosis factor-a, stimulate ferritin production in the media of cultured cells (TNF-a) [24]. This increased secretion was inhibited by co-treatment with the transcriptional inhibitor dichlorofuranosylbenzimidazole, indicating that these cytokines transcriptionally up-regulate ferritin and its secretion [25].

Hepatocytes transfected with the ferritin L cDNA secreted the protein through a canonical secretory route. However, additional study is required to identify the mechanisms by which ferritin enters the secretory system since no signal peptide sequence stimulates ferritin secretion [26]. Ferritin synthesis in the medium of cultured cells is stimulated by iron and the cytokines interleukin-1 (IL-1) and tumour necrosis factor-a (TNF-a). Co-treatment with the transcriptional inhibitor dichlorofuranosylbenzimidazole suppressed this enhanced secretion, demonstrating that these cytokines up-regulate ferritin and its secretion through transcriptional means. Reduced blood iron, increased iron in macrophages, and reduced iron absorption from food all characterize anaemia of inflammation, which is caused by an increase in hepcidin expression triggered by inflammatory cytokines. On the other hand, hereditary hemochromatosis is characterized by abnormal hepcidin expression regulation owing to genetic abnormalities, leading to elevated blood iron, decreased macrophage iron, and increased iron absorption from food [27-30].

3. EXTRACELLULAR FERRITTIN ROLES

Few, if any, research have directly evaluated the effects of exogenous injection of serum ferritin due to the challenges in extracting serum ferritin in sufficient amounts. Exogenous tissue ferritin, however, has been the subject of research by numerous scientists [31]. According to studies, extracellular ferritin can be an iron carrier to deliver iron to cells. A single ferritin molecule may sequester up to 4500 iron atoms, making it

potentially an extremely effective iron delivery system compared to transferrin, which can only carry a maximum of 2 iron atoms [32]. Although serum ferritin, considered iron-poor, transports far less iron than this, it can still greatly impact how much iron is delivered. Chuffer cells loaded with iron were investigated by Sybille et al. for the release of ferritin. According to their findings, these cells' iron content was released into the culture medium as ferritin within 24 hours, making up around 50% of it. When isolated hepatocytes were cultured in this conditioned medium, the released ferritin was readily assimilated by the cells. According to the authors' calculations, this effective process might allow one hepatocyte to amass approximately 160,000 iron molecules every minute. This research shows that exogenous ferritin can serve as a very effective iron delivery system [33].

It has been demonstrated that ferritin, released by macrophages, can serve as an iron supply for erythroid precursor cells, even though erythroid cells typically take up iron via the transferrin-transferrin receptor route [34]. The authors of this study demonstrated that, in the absence of transferrin, monocyte-derived macrophages delivered adequate iron for the proliferation of erythroid precursor cells using a two-phase culture methodology. Although the precise mechanism governing the uptake of ferritin by erythroid cells has not been fully described, receptor-mediated endocytosis may play a role in this procedure. Iron transport to the developing erythrocyte is most likely mostly mediated by the transferrin route [35].

A cell surface receptor must be imagined for extracellular ferritin to perform a physiological function. Ferritin has been found to connect to many distinct cell types in a storable manner over a long period. A saturable ferritin binding site was discovered by Fargion et al. on the surface of human lymphocytes. H ferritin, not L ferritin, was the only bound [36]. Additional research revealed that approximately 30% of CD+ and CD8+ T-lymphocytes and most B cells could bind. It has been established that ferritin's binding to lymphocytes reduces cell growth. Ferritin has also been seen to attach specifically and saturable to liver cells, brain oligodendrocytes, enterocytes, and erythroid precursor cells. While the second type of ferritin receptor had a selective affinity for H ferritin, the first type of ferritin receptor had identical binding affinities for ferritin H and L. The proliferation and colony formation of cells expressing H receptors were reduced when H ferritin was added to the culture medium [37]. Interestingly, liver lipocytes that are active but not dormant also express a particular H ferritin receptor. Through this receptor, ferritin can be metabolized by activated lipocytes. The authors hypothesize that the H ferritin receptor on the surface of activated lipocytes may mediate the transfer of iron from the outside to lipocytes, activating them because activated lipocytes are in charge of increased collagen production and liver cirrhosis in many iron overload diseases.

Exogenous ferritin binding to cell surface receptors has also been suggested to represent a significant route for transferring iron to the brain [38]. However, most cells' primary iron import pathway is the transferrin-transferrin receptor pathway. Other iron uptake systems independent of transferrin must exist because oligodendrocytes need iron to build myelin and contain more iron than any other cell in the central nervous system. Connor and colleagues discovered an H ferritin receptor that could take up ferritin through receptor-mediated endocytosis on the cell surface of oligodendrocytes. They suggested that the primary source of iron for oligodendrocytes is iron supplied by ferritin [39]. Although the specificity for H- or L-ferritin was not specifically investigated, other investigations have shown that ferritin binds to various cell types. The membranes of the placenta also contain a ferritin receptor. Interestingly, compared to pregnant women with normal iron status, pregnant women with mild or severe iron shortage have much more ferritin receptor binding sites [40]. Despite numerous studies identifying ferritin-binding sites on cells, mouse T cell immunoglobulin domain and mucin-domain was the first ferritin-binding cell surface receptor to be cloned2 (TIM-2). Transmembrane protein TIM-2 is expressed in T cells, B cells, the liver, and the kidney. Although TIM-1 and TIM-2 have sequence homology, TIM-2 has no known human ortholog. T-cell activation has been demonstrated to be inhibited by TIM-2. In a search for TIM-2 ligands, the ferritin H receptor TIM-2 was found. Ferritin H is internalized into endosomes due to its interaction with TIM-2 on the cell surface. This work supports the idea that TIM-2 delivers ferritin, which contains iron, into cells. Ferritin-TIM2 was proposed as the main route for iron uptake by oligodendrocytes since there is no discernible Tf-TfR pathway for iron transport in these cells [41].

Scara5 is a recent ferritin cell surface receptor discovered by Li et al. A scavenger receptor, Scara5, can bind various ligands. Scara5 preferentially binds ferritin L as opposed to TIM-2, a ferritin receptor. Scara5 contributes significantly to kidney organogenesis, perhaps by supplying cells with iron. The 1ors also demonstrated how ferritin with iron linked to Seara 5 and underwent endocytosis, releasing iron into the cytoplasm. Recently, a human ferritin receptor was discovered. Human TfRl was recognized by Li et al. as a cell surface receptor for H ferritin using expression cloning [42]. There was no evidence of binding to L ferritin. Because ferric transferrin could only partially prevent the binding of H ferritin to TfRl, the binding sites for transferrin and ferritin may not completely overlap on the receptor. Most H ferritin's binding to the cell surface is caused by its association with TfRl, which also causes H ferritin to be transported to lysosomes and

enterosomes. Investigations are currently being made into how iron is liberated from ferritin for cell usage. The possibility that iron could leave the protein through gated pores has been raised.

Kidane et al. demonstrated that iron release requires lysosome-dependent ferritin breakdown (DFO) with the use of the iron chelator deferoxamine. Domenico et al. corroborated this conclusion after treating mice with the more permeant iron chelators deferiprone and deferasirox, which were shown to trigger ferritin breakdown in the proteasome and iron release from ferritin before its destruction. They detailed an alternative method of iron extraction. It will be exciting to trace iron trafficking pathways after ferritin iron release [43].

4. FERRITTIN AS SIGNALING MOLECULE

Extracellular ferritin has recently been shown to play a new role in hepatic stellate cells as a pro-inflammatory signalling molecule by Ruddell et al. They discovered that cells exposed to ferritin activated a process that involved the activation of Fib, P.B. kinase phosphorylation, protein kinase C zeta, and MAP kinase. Nek in the tumour was activated, which increased the expression of pro-inflammatory mediators such as iNOS and interleukin 1 beta. Interestingly, this activity was independent of ferritin's iron level, indicating that exogenous ferritin may take on other tasks outside its traditional one as an iron-binding protein [44].

The impairment of cell-mediated immunity in individuals with hematologic malignancies, such as Hodgkin's disease and acute leukaemia, has long been recognized. Serum ferritin levels are also high in these patients. This implied that serum ferritin and immunity might be related. Early in vitro research demonstrated that ferritin modifies body immunological function by preventing lymphocyte activity. Splenic ferritin reduced the activation of lymphocyte cells by phytohaemagglutinin (PHA) and concanavalin A (Con A) in human lymphocytes. Later in vivo research provided additional evidence that ferritin suppresses immunity. Recombinant human ferritin H was administered intravenously to mice by Broxmeyer et al. to research the impact of ferritin on haematopoiesis [45]. They discovered that ferritin H dramatically reduced granulocyte-macrophage, erythroid, and multipotent progenitor cell proliferation and numbers. Interestingly, the myelosuppressive function of ferritin H was dependent on its ferroxidase activity since ferritin H mutations that inactivate its ferroxidase activity eliminates the myelosuppressive activity. Ferritin L, which has no ferroxidase activity and hence has no influence on myelopoiesis, supports this finding.

An iron source called heme reversed ferritin's inhibition. The scientists hypothesized that the myelosuppressive properties of ferritin were caused by its suppression of cellular transferrin iron uptake because iron is necessary for cell proliferation and differentiation, especially in lymphoid and myeloid cells. Chemokines are a family of proteins that affect different leukocyte lineages, chemotactic and activating. They are crucial for T helper cell responses, hematopoiesis, hemostasis, and angiogenesis [46]. It has been proposed that ferritin H can contribute to immune suppression in at least part by stimulating the synthesis of IL-10 in lymphocytes, even if the precise methods by which ferritin inhibits immunological responses are still completely unclear (IL-10 have been shown to inhibit IL-2 production as well as lymphocyte proliferation).

Ferritin's anti-immune action is mediated via signalling mechanisms that are yet poorly understood. However, it is tempting to hypothesize that ferritin H and TIM-2 may work together to inhibit the immune system because TIM-2 has been identified as a particular cell surface receptor for ferritin H. The T cell immunoglobulin and mucin domain (TIM) gene family, which plays a role in the control of immunological responses, includes TIM-2. On mouse chromosome 11 and human chromosome 5, the TAPR locus (T cell and airway phenotypic regulator) contains the TIM gene family. Several immune-related disorders are linked to genetic polymorphisms in the TAPR locus. Human TIM-I and TIM-3 have been reported to include a variety of polymorphisms; these polymorphisms have been linked to asthma and other allergy illnesses [47].

5. FERRITTIN IN INFAMMATION

Serum ferritin is non-specifically increased in several inflammatory conditions, such as chronic kidney disease, rheumatoid arthritis and other autoimmune disorders, acute infection, and cancer. It is well recognized as an acute phase reactant and marker of acute and chronic inflammation. However, ironically, these stores are sequestered and unavailable for hematopoiesis, contributing to the well-known inflammation anaemia. The raised ferritin in both situations indicates greater total body iron stores. It is thought that this relative iron deficit in inflammation and cancer developed as a defence mechanism to prevent microbes and tumours from utilizing serum iron. Serum ferritin increases are notable in two clinical entities, Still's illness and hemophagocytic syndrome [48].

6. FERRITTIN AND ANGIOGENESIS

In the course of looking for ferritin binding partners in human serum, high molecular weight kininogen (H.K.), a 120 kDa abundant plasma protein previously identified as a co-factor in the intrinsic coagulation cascade, was shown to interact with ferritin. H.K. is a ferritin-interacting protein. Bradykinin (B.K.) and two-

chain high molecular weight kininogen are independently active proteins created when the serine protease kallikrein cleaves H.K. (H.K.). B.K., a peptide with nine amino acids and fast action, causes NO release, discomfort, and vasodilation [49].

B.K. is a peptide that promotes angiogenesis. The other byproduct of the H.K. cleavage, Hake, on the other hand, is antiangiogenic. In numerous physiological and pathologic processes, including wound healing, the menstrual cycle, and tumour growth and metastasis, angiogenesis—forming new blood vessels from pre-existing ones—plays a crucial role. Various pro- and antiangiogenic elements work in harmony to control the process of angiogenesis. The two HK.cleavage products have interestingly contrasting functions in angiogenesis: While HK.a inhibits vessel development, B.K. encourages it. By directly interacting with both H.K. and H.K.a, ferritin is a newly identified angiogenic regulator. According to deletion mapping and solid phase binding tests, ferritin directly interacts with the light chain of H.K. with a Kd of 140 nM. Ferritin suppresses the production of B.K. and H.K., which lowers the levels of these angiogenic regulators. It also decreases the cleavage of H.K. by kallikrein and two inflammatory proteases, neutrophil elastase and mast cell tryptase [50].

Ferritin further binds HK.a directly. In actuality, ferritin's affinity for HK.a is ten times greater than that of H.K. Ferritin binds to HK.a's domain 5. This domain, revealed when H.K. is cleaved to liberate B.K. and create HK.a, is in charge of H.K.a's antiangiogenic capabilities. Ferritin inhibits the effects of HK.a by attaching to its antiangiogenic domain, which promotes the formation of new blood vessels. Ferritin supplementation considerably increases intratumor blood vessel density in a mouse tumour model where HK.a inhibits the formation of tumour blood vessels. Serum ferritin levels considerably increase during inflammation and some types of cancer, in which physiologic and pathologic angiogenesis occurs. This spike in serum ferritin levels may have a physiological basis in ferritin's proangiogenic activity, which it exerts through binding to HKJHK.a. This proangiogenic activity allows ferritin to operate as an angiogenic modulator, promoting the formation of new blood vessels. This could be a pathogenic response in the case of tumour growth or a healthy response in the case of inflammation and wound healing [51].

Other ferritin binding partners than H.K. have been discovered in serum and plasma, including apo lipoprotein B38, a-2- macroglobulin(a 2M))44.4 5, anti-ferritin autoantibody 38, 39, and fibrinogen. Ferritin postsynaptically prevents the release of Apo lipoprotein B by interacting with it. A 2M is a large plasma protein that can bind numerous ligands and remove them from the bloodstream via endocytosis mediated by a 2.1 receptor. There may be a mechanism for cellular uptake and elimination of ferritin from circulation when a 2M was discovered to bind ferritin. Also found in canine serum were ferritin autoantibodies and a ferritin immune complex, which may aid in the removal of circulating ferritin [52].

7. FERRITIN IN CANCER

Numerous cancers have increased serum ferritin levels. In some instances, this general rise in ferritin levels in the blood is also accompanied by a change in ferritin composition toward more Hrichspecies. For instance, ferritin H makes up most of the serum ferritin in malignant histiocytosis. Uncertain mechanisms underlie these alterations. The release of ferritin by the tumour has been directly connected to increased serum ferritin in neuroblastoma. In this research, ferritins from human beings were found in the serum of naked mice who received transplants of human neuroblastoma [53].

However, the serum ferritin ratio of neuroblastoma patients did not change, suggesting that the quantity or type of ferritin generated by tumours is inadequate to affect the overall composition of serum ferritin. Patients with a new breast cancer diagnosis, local recurrence, or distant metastases had greater blood ferritin levels before surgery. Malignant epithelium had an abundance of ferritin, whereas healthy epithelium and connective tissue contained far less protein. Cytosol extracts from mammary carcinomas exhibited a 10-fold increase in tissue ferritin compared to normal breast tissues. However, a different study found that ferritin was largely present in the stroma and histiocytes surrounding cancerous cells, suggesting that increased serum ferritin levels in breast cancer patients may be due to stromal reactivity rather than stromal reactivity than tumour formation. It is generally established that too much iron changes how different T-lymphocyte subsets are distributed, inhibits the activity of helper T (CD4) cells, and inhibits the ability of macrophages and monocytes to destroy tumours. Iron excess in people with hereditary hemochromatosis raises CD8:CD4 ratios because it boosts suppressor T (CD8) cell numbers and activity while decreasing CD4 cell numbers and activity [54].

Therefore, it is believed that the extra iron may hinder these mechanisms' ability to monitor cancer cells. Although there were not many women with hemochromatosis48, two cohort studies of malignancy in hemochromatosis patients did not find an elevated risk of breast cancer. Ferritin is a serum maker for the presence of cancer, but no research has yet shown that it also plays a role in the aetiology of the disease. However, Kabat and Rohan have noted that the increased risk of breast cancer in postmenopausal women is consistent with the idea that greater iron storage may aid in cancer development.

Ferrous iron (Fe2+), which can catalyze the creation of the hydroxyl radical (*O.H.), is created when ferric iron (Fe3+), liberated from ferritin and hemosiderin, is reduced to ferrous iron (Fe2+). The hydroxyl radical is a potent oxidizing agent that can encourage DNA strand breakage, mutagenesis, lipid peroxidation, oncogene activation, and tumour suppressor gene suppression. There is conflicting evidence regarding the role of lipid peroxidation products in breast cancer. It is hypothesized that iron interacts with recognized carcinogens, particularly ionizing radiation, ethanol, and oestrogen. Iron overload makes reactive oxygen species generation, lipid peroxidation, and DNA damage more likely. It may be possible to lower this risk by using natural or synthetic chelating agents, such as 37Ferritin, as a therapeutic tool if subsequent research reveals that excessive body iron levels contribute to the development of breast cancer. The doctor can use ferritin to assess common disease states such as iron deficiency anaemia and acquired and genetic iron overload diseases like hereditary hemochromatosis and prolonged transfusion therapy. Serum ferritin is undoubtedly the most helpful marker in the majority of populations. It is typically included in a panel of many blood tests frequently ordered to identify and treat these diseases, albeit there are significant limitations.

Anaemia from iron deficiency. Both industrialized and developing nations experience high rates of iron deficiency anaemia. To diagnose anaemia, doctors frequently request serum ferritin, which indirectly measures the body's total iron storage. Low blood ferritin levels are far less intrusive than the standard gold method of performing a bone marrow biopsy to determine stainable iron, which is highly specific for iron deficiency anaemia. Serum ferritin, which outperformed red cell protoporphyrin, transferrin saturation, mean cell volume, or red cell distribution with an area under the receiving operating characteristic curve of 0.2, was by far the most effective test for the diagnosis of iron deficiency, according to a systematic review of the diagnostic values used in the evaluation of iron deficiency anaemia.

8. NEUROLOGIC ASSOCIATIONS

Low blood ferritin levels have recently been linked to neurally mediated syncope in kids and teenagers, and they may play a significant role in the pathogenesis of this prevalent condition. Long recognized as a sign of iron deficiency in very young infants, breath-holding spells are a type of early childhood neurally mediated syncope. The fact that pregnant and anaemic people frequently experience restless legs syndrome in adults suggests that serum ferritin may play a part in the pathogenesis of this illness. However, current information suggests that symptoms and serum ferritin and CSF ferritin have a more complicated association.

9. FERRITTIN IN CHRONIC KIDNEY DISEASE

Serum ferritin is not a good predictor of available iron in people with chronic renal impairment. Hyperferritinemia is a misleading sign of iron accumulation under these conditions. About half of all patients on maintenance haemodialysis have serum ferritin levels higher than 500 ng/ml; however, this does not mean that iron is bioavailable for erythropoiesis. There was an increase in ferritin levels in almost a third of hemodialysis patients. C-reactive protein (CRP) levels and the malnutrition-inflammation score were higher in haemodialysis patients with serum ferritin levels over 800 ng/ml.

10. FERRITTIN IN LIVER DISEASE

Iron reserves are reflected in the serum ferritin levels of alcoholics with moderate liver disease. Still, liver iron levels do not indicate iron stores in alcoholics with severe liver disease. Hepatitis C virus infection is often linked to elevated iron parameters when hemochromatosis mutations co-occur. As Hepatitis C progresses, fibrosis and, eventually, liver cirrhosis are common outcomes. Iron is thought to be a major co-morbid component in this progression. Saturation levels of ALT, iron, and transferrin were associated with hepatic iron stain and serum ferritin. Serum ferritin has been shown to independently predict severe hepatic fibrosis in individuals with chronic Hepatitis C infection. However, this finding was not supported in the more recent Korean dataset. Among dialysis patients infected with BCV, ferritin is the most reliable biomarker of liver impairment.

11. FERRITTIN IN HEMOCHROMATOSIS

The predominant clinical symptom of hemochromatosis, cirrhosis, is strongly predicted by serum ferritin. According to several investigations, liver cirrhosis is uncommon in hemochromatosis individuals with blood ferritin levels less than 1000 micrograms/litter. Acquired iron contains ferritin. In non-hereditary iron overload disorders, including transfusion-associated iron overload in myelodysplastic syndromes, thalassemias, and hemoglobinopathies, elevated serum ferritin also predicts end-organ involvement. Following a transplant, ferritin levels. Although there is no agreement on what constitutes iron excess in these individuals, several studies have demonstrated that the presence of iron overload before an allogeneic or an autologous hematopoietic stem cell transplant is related to complications and lower survival. In a group of Italian patients

receiving an allogeneic hematopoietic stem cell transplant, high ferritin levels (>1000 ng/ml) were found to be an independent risk factor for developing liver dysfunction, as determined by abnormal liver function tests.

Although iron overload is less common in recipients of solid organs than in patients with haematological malignancies due to less frequent red cell transfusions, the problem has been resolved following solid organ transplantation. When compared to healthy controls, lung transplant recipients had considerably higher ferritin concentrations in their bronchoalveolar lavage fluid, which raised the possibility that the allograft would experience iron-induced oxidative stress. In patients with renal allografts, serum ferritin was a valid indicator of the histological diagnosis of hepatic hemosiderosis. Multiple blood transfusions (>40 units) before transplantation were associated with a 3-fold relative risk for mortality, according to a ten-year follow-up study of renal transplant recipients with serum ferritin levels >1,100 ng/ml.

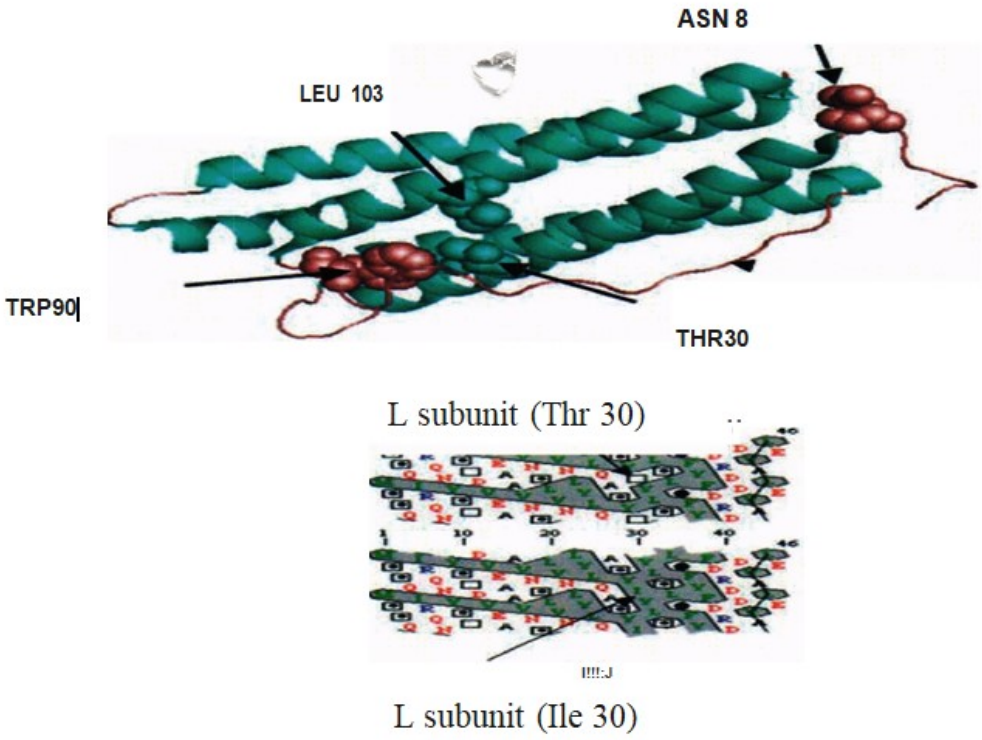

Figure 1. Ferritin's 3D structure. Hydrophobicity at the N-terminus resulted from the Thr30 mutation and its location in the L ferritin subunit crystal structure. Figure A shows the localization of Thr30 inside the L ferritin crystal and some of the surrounding features. Fragments of amino acids As for the helical structure, Thr 30 is on helix A, Trp90 is on the B-C loop, and Leu 103 is on helix C. It also shows the glycosylated Asn. To better understand the L ferritin subunit crystal structure described in reference 18, the Pymol programme was used for analysis. (B) A helix hydrophobicity cluster analysis for wild-type L and the p alleles. The hydrophobic cluster is elongated when isoleucine is substituted for threonine at position 30. (hydrophobic residues are indicated in green, and the hydrophobic cluster is encircled).

12. PATHOPHYSIOLOGY

Type 2 diabetes mellitus and iron metabolism have a reciprocal link. Both iron and glucose metabolism have an impact on several iron metabolic pathways. Iron affects glucose metabolism. Even with considerable iron excess, it is becoming increasingly understood. Additionally, there was a strong correlation between obesity and the circulating ferritin level. Iron is a strong prooxidant that raises the level of oxidative stress in cells, which inhibits insulin's internalization and activities and causes hyperinsulinemia and insulin resistance. The synthesis of ferritin is positively influenced by free iron, while the release of iron from ferritin is accelerated by oxidative stress. Insulin sensitivity is decreased, and diabetes mellitus problems develop early from iron overload. In their study, Qian et al. demonstrated that bloodletting, which reduced serum ferritin levels by 50%, increased glycemia and insulin sensitivity in people with type 2 diabetes mellitus. Therefore, insulin resistance may be a second factor contributing to hyperglycemia after iron overload and damage to pancreatic beta cells. Furthermore, hyperferritinemia in type 2 diabetes mellitus may be caused primarily by anomalies in ferritin metabolism following glycation in a hyperglycaemic condition.

As glycaemic management affects serum ferritin levels, glycated ferritin has a prolonged serum half-life. Transferrin's ability to bind ferrous ions is reduced by glycation, which also increases the amount of free iron and promotes ferritin synthesis. Additionally, it is known that glycated holotransferrin promotes the synthesis of free oxygen radicals like hydroxide, which intensify the oxidative effects on iron. In their work, Nan Hee Kim et al. demonstrated that serum ferritin was the third-strongest predictor of serum insulin (after age and BMI) and the second-strongest predictor of blood glucose (after BMI) in regression models.

In their investigation, Earl S. Ford et al. discovered that serum ferritin content was significantly and positively linked with glycated hemoglobin9. Glycated ferritin has a longer serum half-life. Additionally, even before the onset of severe diabetic Mellitus, insulin resistance, which is compensated by hyperinsulinemia, develops and correlates favourably with signs of iron overload and SF5. Regular blood donations cause iron levels to fall, which lowers postprandial hyperinsulinemia in healthy volunteers and increases insulin sensitivity. In chronically transfused individuals with significant thalassemia, insulin resistance is positively correlated with the total units of blood transfused, splenomegaly, and S.F.

In type-2 diabetes mellitus, phlebotomy is followed by a decrease in blood sugar, cholesterol, and triglycerides, as well as an improvement in beta cell secretion and peripheral insulin action. In epidemiological studies, high body iron levels have also been linked to type 2 diabetes, insulin resistance, and diabetic retinopathy. Hyperferritinemia was also linked to diabetic retinopathy in a study of poorly controlled diabetic patients. Increased body iron reserves may have a comparable impact on diabetic nephropathy and vascular dysfunction. The current review covers elevated serum iron levels' effects on type 2 diabetes patients. Serum ferritin and diabetes mellitus showed a significant association, according to Wrede et al. Increased body iron storage has lately been linked to the onset of type 2 diabetes, gestational diabetes, glucose intolerance, and insulin resistance syndrome. Regular blood donations cause the body to store less iron, which lowers postprandial hyperinsulinemia and increases insulin sensitivity. In type-2 D C, phlebotomy is followed by a decrease in serum glucose, cholesterol, and triglycerides and an improvement in beta cell secretion and peripheral insulin action. The same association has also been found in epidemiological investigations. Hyperferritinemia is a comorbidity of diabetic retinopathy, diabetic nephropathy, and vascular dysfunction in D.M. patients with poor management.

It's critical to understand that elevated levels of Qf iron over physiological requirements have no beneficial effects on patients. However, an absence of research, mainly from India, demonstrates direct evidence that controlling D.M. in patients with iron excess is challenging. However, there are few indirect shreds of evidence from the western region suggesting that iron overload negatively affects D.M. Finding such an association in the Indian population has significant therapeutic implications because anaemia is a problem that affects the underlying diabetic condition and is actively being prevented and treated at the level of the government, the community, and the medical profession in India. Determining the link between serum ferritin (S.F.) and serum insulin (S.I.) levels in type-2 D.M. and the impact of body iron reserves as evidenced by various biochemical parameters and diabetic complications in an Indian population were the goals of the current investigation. Numerous investigations showed a statistically significant proportional association between elevated body iron reserves, as shown by S. ferritin levels and S. insulin levels. Hyperinsulinemia, which develops early, even before the onset of frank diabetes mellitus and has a strong correlation with I.R. (insulin resistance), compensates for I.R. The results support those of Wrede et al.. They found a strong association between S.F. and the existence of insulin resistance criteria in a sizable representative population.

Similar indirect evidence that insulin resistance develops early and correlates favourably with the total number of blood transfusions and serum ferritin in continuously transfused thalassemia major patients was reported by Suvama et al. from India. In the general population, Fernandez et al. discovered that higher iron reserves might be linked to glucose intolerance, type 2 diabetes, and gestational diabetes. After undergoing phlebotomy, Facchini observed a considerable decrease in serum insulin levels and an improvement in insulin sensitivity. Following phlebotomy, Dymock et al. found a substantial reduction in the daily dosage of insulin. Similarly, Dmochowski et al. found a negative correlation between serum ferritin concentration and insulin sensitivity in thalassemic individuals.

According to Jiang et al., iron excess results in the hydroxyl radical's development, which damages cells and promotes insulin resistance. This theory is supported by the observation that deferoxamine, a chelating drug with antioxidant characteristics, improves fasting blood glucose in continuously transfused thalassemia major patients. It has recently been proposed that iron and transferrin cause I.R. of glucose transport in adipocytes. These theories, however, still need to be proven in the future. We observed a favourable link in the patients between higher S.F. and poorer glycemic control as indicated by higher HbA1C, corroborating the findings of Eschwegeet al. Insulin resistance, hypertension, dyslipidemia, obesity, type 2 D.M., and accelerated cardiovascular disease are all symptoms of the metabolic syndrome. A suggested IRS component is iron reserves represented as concentration.

Additionally, S.F. concentration is negatively correlated with HDL concentration and directly connected to serum T.G., another element of the IRS. According to Dymock et al., increased body iron levels impact diabetic nephropathy and vascular dysfunction. Vascular damage and poor glucose control are present in patients with elevated S.F. Ralpha & Fronzo have noted insulin resistance in these individuals. According to the findings above, a strong association between elevated S.F. levels and diabetic nephropathy was discovered in our investigation. Patients with poorly managed diabetes who participated in a Cantur KZ et al. experiment showed hyperferritinemia. Several functional problems are detected in the microvasculature of the nerves of diabetic patients, even though chronic hyperglycemia appears to be the main component in the aetiology of neuropathy. These include metabolic syndrome characteristics, insulin resistance, high systolic blood pressure, and diabetic dyslipidaemia.

13. FUTURE PROSPECTS

Inflammatory markers and an indicator of bodily iron reserves have been associated with ferritin. In several epidemiological research, serum ferritin was the third-strongest predictor of serum insulin and the second-strongest predictor of blood glucose (behind BMI) in regression models (after BMI and age). Additionally, its content negatively correlated with HDL2 cholesterol and positively correlated with plasma triglycerides and Apo lipoprotein B levels. According to our theory, serum ferritin may signify insulin resistance. After Kaye al. initially examined the potential relationship between ferritin and D.M. in 1993, several investigations centred on this topic. High levels of ferritin were found in diabetics in a 1999 study conducted by Ford and his colleagues on 9486 diabetic people in the United States. Another research by Kwant on the prevalence of the hemochromatosis gene's C282Y mutation found that type 2 D.M. had a greater incidence of this mutation, which might be interpreted as evidence for a connection between these two conditions.

In 1998, Fernandez looked into the correlations between healthy patients' blood ferritin levels and their glucose tolerance test and insulin sensitivity scores. Serum ferritin may be a sign of insulin resistance, according to this study's correlations between it and diastolic blood pressure, HDL, glucose area under the curve, and insulin sensitivity. Kim et al. have also reported on the same outcomes. Our findings didn't support their assertion that serum ferritin may potentially act as a standalone predictor of poor metabolic management in diabetes individuals. This discrepancy may be the result of our exclusion criteria, which included severe diabetes complications and anaemia, which were not considered in other investigations.

Regarding ferritin's function in D.M., several ideas exist. At least in certain cases of diabetes, pancreatic damage brought on by some degree of subclinical hemochromatosis has been proposed. As indicated above, some have identified ferritin as a marker for insulin resistance, whereas others have discovered it to be a simple indicator of pancreatic inflammation. In diabetic patients, the impact of ferritin decrease by bloodletting on insulin sensitivity and HbA1c levels was investigated by Fernandez et al. Although the potential role of ferritin in D.M. pathogenesis was confirmed in this study by the positive effect of ferritin reduction on blood glucose control, the use of bloodletting might also affect total haemoglobin levels and HbAlc, making it inappropriate to use HbAlc as a marker of blood glucose control. Recently, little research looked into how chelator medications like Desferal affected the management of type 2 diabetes. In this sense, there are several outcomes. According to research, those at high risk for atherosclerosis had greater ferritin levels. Insulin resistance may cause elevated ferritin levels in atherosclerotic individuals since it is thought to be the primary factor in the pathophysiology of atherosclerosis.

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