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Association of Iron Profile with Type 2 Diabetes Mellitus:Review

Khaldoon Jasim Mohammed*[1], Salam Kitab Rubat[2], Ahmed Falah Imran[3]

[1,3]Department of Chemistry, College of Science for Girls, University of Babylon, Babylon, Iraq.

[2]Animal Production Department, College of Agriculture, Kirkuk University, Kirkuk, Iraq.

ABSTRACT

This minireview assesses the correlation between iron profile levels and type 2 diabetes mellitus. Iron, ferritin, transferrin saturation, and total iron-binding capacity (TIBC) are examples of iron profiles. Every study included in this review shows that type 2 diabetics' blood serum has less iron overall and less iron-binding capacity. Conversely, the same studies' findings showed that individuals with type 2 diabetes had higher levels of ferritin in their blood serum. In terms of transferrin (iron) saturation, a number of studies show that it is rising, while a smaller number shows that it is falling in the blood serum of those who have type 2 diabetes. These investigations led to the conclusion that there is substantial evidence linking the iron profile to type 2 diabetic mellitus (T2DM). Reduced transferrin levels are connected to a lower risk of Type 2 Diabetes Mellitus, but higher serum iron, ferritin, and transferrin saturation are associated with an increased risk. There is also genetic evidence that links elevated systemic iron status to a higher risk of type 2 diabetes.

KEYWORDS: Diabetes Mellitus, Transferrin, Total Iron-Binding Capacity, Iron.

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INTRODUCTION

The components that comprise the iron profile are serum ferritin, total iron binding capacity (TIBC), transferrin saturation, and iron content. Iron stores are shown by serum ferritin levels, while the quantity of iron attached to transferrin is indicated by transferrin saturation. The blood's iron content is measured by iron concentration. Daily fluctuations are noteworthy, particularly in the case of iron and ferritin

[1]. Variations in genetics can impact iron metabolism, which in turn can impact iron status and the likelihood of iron excess or insufficiency. These markers can be used to determine iron status, although they can change daily and are affected by things like inflammation and physical exercise [2]. Tests for iron profiles are used to evaluate several facets of the body's iron stores. These tests are crucial for the diagnosis of diseases associated with excess or insufficient iron. The following justifies iron profile testing: Iron deficiency: determining iron levels is essential for the diagnosis of iron deficiency anemia, a prevalent disorder marked by low iron and reduced synthesis of red blood cells [3]. Iron Overload: These tests aid in the diagnosis of diseases like hemochromatosis, a condition in which the body absorbs excessive amounts of iron, causing it to build up in organs [4]. Inflammatory Conditions: Iron profile testing can assist in distinguishing between anemia, a chronic illness brought on by persistent inflammation, and iron shortage. Treatment Monitoring: They're employed to keep an eye on how well iron supplements or other treatments for problems related to iron are working [5]. Risk Assessment: Iron profile testing can assist in determining the probability of developing diseases like cancer and diabetes mellitus.

Diabetes is now seen as a serious global disease that affects people. Increased ferritin levels are associated with an increased risk of constructing type 2 diabetes mellitus (T2DM) [6]. The chance of acquiring type 2 diabetes is increased by 14% for every 100 µg/l increase in serum ferritin6. Additionally, there is a link between an elevated risk of incident T2DM and insufficiently low levels of hepcidin, a hormone that controls iron homeostasis. These results imply that ferritin and hepcidin levels, as well as other iron profile tests, might be helpful in identifying those who are highly susceptible to type 2 diabetes [7,8]. To prove causation and ascertain the possible advantages of lifestyle or treatment measures, more investigation is necessary. Because type 2 diabetes mellitus is becoming more commonplace globally, it is important to conduct this retrospective study to understand how iron profiles relate to diabetes mellitus. This will help to

prevent and/or manage diabetes by utilizing micronutrients in food or supplements to lower the risk of complications from the disease.

IRON AND TYPE 2 DIABETES

Iron is an essential mineral for oxygen transportation, synthesis of DNA, and energy production. Iron deficiency is a primary nutritional problem, impacting 66% of women and children in poor nations. It can lead to anemia, compromised immune systems, decreased work capacity, and impaired learning [9]. Iron deficiency can be caused by blood loss, eating a bad diet, or not getting enough iron from food. Oral or intravenous iron therapy is one form of treatment, yet too much iron can be harmful [10]. Although current parenteral iron formulations allow for quick and safe total-dose iron replacement, oral iron therapy remains the primary line of treatment. Fortification, supplementation, and dietary changes can help prevent iron deficiency [11].

Type 2 diabetes mellitus is influenced by iron. In T2DM patients, hemoglobin A1c (HbA1c) levels are impacted by iron deficiency anemia (IDA). In anemia patients with type 2 diabetes, iron replacement therapy can lower HbA1c [12]. On the other hand, ferritin levels are enhanced in T2DM patients, and a higher risk of T2DM is linked to increased iron intake [13]. Consequently, elevated serum ferritin levels stand alone as a risk factor for type 2 diabetes mellitus [14]. Iron resistance and insulin resistance are two of the many mechanisms involved in the intricate relationship between iron and type 2 diabetes. As such, people with type 2 diabetes should have their iron level closely checked [15]. Hemoglobin A1c (HbA1c) levels in people with type 2 diabetes mellitus (T2DM) are impacted by iron deficiency anemia (IDA). According to a study, iron replacement treatment dramatically raised HbA1c in T2DM patients with IDA. On the other hand, raised ferritin levels, a biomarker indicating higher body iron stores, are seen in T2DM patients. Elevated serum ferritin levels have been linked to an increased risk of type 2 diabetes. The basic processes driving the iron-type diabetes mellitus connection remain incompletely understood. In order to reduce the risk of type 2 diabetes and associated complications, it is crucial to take iron status into account when interpreting HbA1c concentrations in T2DM patients and to keep an eye on their iron levels [16,17,18]. While low iron levels have been linked to T2DM, according to certain research, iron overload might contribute to the pathophysiology of the condition. Uncertainty surrounds the causes of low iron levels in type 2 diabetes [19]. Low iron levels, however, may be the consequence of disruptions in iron metabolism brought on by insulin resistance and chronic inflammation in type 2 diabetes. Low iron levels in people with type 2 diabetes may also be a result of anemia of chronic disease, a condition in which the body's iron reserves are impacted by ongoing inflammation [20]. Type 2 diabetes and iron have a complicated interaction. A diet high or low in iron can have an impact on insulin secretion, glucose metabolism, and the pathophysiology of type 2 diabetes [21]. Oxidative stress, inflammation, and metabolic pathway regulation are some of the mechanisms. Iron levels influence the risk of diabetes via influencing adipocyte phenotype, insulin action, and metabolic rates [22]. Other studies indicate the decrease in serum iron levels in people who have type 2 diabetes (T2DM) can be caused by several factors, including: Increased Oxidative Stress: People with type 2 diabetes frequently have higher levels of oxidative stress, which can lower serum iron levels [23]. Iron Resistance: In T2DM, metabolic disruptions may result in the "iron resistance" phenotype, which can cause signals that regulate iron homeostasis to become dysregulated. Iron overload disorders including primary and secondary hemochromatosis, which can lower serum iron levels, are commonly linked to type 2 diabetes [24]. Reduced serum iron levels can result from elevated ferritin levels, which are linked to type 2 diabetes [25]. Iron deficiency anemia, which can lead to lower serum iron levels, is another condition that T2DM patients may encounter [26]. Iron depletion or bloodletting has been found to improve insulin sensitivity in patients with high-ferritin type 2 diabetes [27]. Research has repeatedly demonstrated a correlation between increased serum ferritin levels, a measure of the body's iron reserves, and insulin resistance. On the other hand, a higher likelihood of insulin resistance has been associated with lower serum iron levels. As an illustration, one study discovered a negative correlation between serum ferritin content and insulin sensitivity, whereas another study indicated that low hepcidin levels in type 2 diabetics were linked to insulin resistance [28]. Furthermore, a study in Chinese, Serum transferrin and soluble transferrin receptor levels were found to be substantially correlated with insulin resistance in children and adolescents [29]. According to these results, insulin resistance and type 2 diabetes may have a pathophysiological role for abnormal iron metabolism.

FERRITIN AND TYPE 2 DIABETES

Ferritin is a protein that stores iron in reserve and protects cells from its harmful effects. It is a protein nanocage that consists of 24 subunits with an iron core. Because of its structure, ferritin can store iron and shield cells from its harmful effects [35]. When cellular ferritin synthesis takes place in the comparatively low amount of free cytosolic iron, ferritin secretion happens. Ferritin has been demonstrated to be induced by Cd (2+), Pb (2+), and Fe (2+), making it an attractive option for heavy metal detoxification. One possible marker for tumor identification and treatment is ferritin [36]. It is related in a number of problems and is essential for iron metabolism [30]. The serum contains ferritin, which is used to determine an individual's iron status. The potential of this substance in tumor identification and therapy has been investigated. Ferritin also plays a role in autoimmune and immunity [31,37]. According to recent studies, ferritin functions as an immunological regulator and a signaling

protein and can be secreted by macrophages [32,33]. Ferritin has also been investigated for its potential in Nano biomedical applications, including tumor diagnosis and therapy [34]. Researchers found [38,39,40] A higher chance of developing type 2 diabetes mellitus (T2DM) has been associated with elevated serum ferritin levels. Participants with type 2 diabetes had a mean serum ferritin level that was noticeably greater than that of the control group. In addition, patients with uncontrolled T2DM exhibit hyperferritinemia. Ferritin and the risk of type 2 diabetes are more closely associated in those with higher levels of high-sensitivity C-reactive protein (hs-CRP). It is unclear exactly what mechanisms underlie this relationship, though. Therefore, further research is required to completely understand the connection between elevated serum ferritin levels and type 2 diabetes, even though there is evidence associating the two [41,45]. Uncontrolled type 2 diabetes patients have hyperferritinemia, and people with controlled type 2 diabetes also show elevated blood ferritin activity. In addition, people with poorly controlled type 2 diabetes have higher serum ferritin levels, which is an independent risk factor for the disease. Patients with type 2 diabetes mellitus consequently have higher serum ferritin levels [42,43]. Elevated blood ferritin levels raise the risk of type 2 diabetes by being associated with reduced insulin sensitivity and compromised beta cell activity [44,46]. The relationship between serum ferritin levels and type 2 diabetes may also be influenced by genetic variables [47]. Type 2 diabetes development may be influenced by dysregulation of iron metabolism and elevated serum ferritin activity [48]. Therefore, serum ferritin levels increase in patients with type 2 diabetes mellitus.

On the other hand, low ferritin levels in type 2 diabetes are less common. Some studies that found a deficiency in ferritin, generally speaking, type 2 diabetes is not linked to low ferritin levels. Conversely, research has repeatedly demonstrated that elevated ferritin levels are associated with a higher risk of developing type 2 diabetes. Insulin resistance and a higher risk of type 2 diabetes are linked to elevated ferritin levels [49]. Low ferritin levels in type 2 diabetics may be brought on by long-term medical conditions, malnutrition, or blood loss [50]. Even so, the research does not provide strong evidence for these connections. The precise causes of decreased ferritin levels in individuals with type 2 diabetes require more investigation.

TRANSFERRIN (IRON) SATURATION AND TYPE 2 DIABETES

The protein transferrin is responsible for moving iron throughout the body. It interacts with different types of cells by binding to iron and supplying them with the iron required for their metabolic functions[51]. On the plasma membrane surfaces of all organs are transferrin receptors, which interact preferentially with diferric transferrin [52]. Humans have a daily total plasma iron turnover of roughly 36 mg. Two homologous domains make up transferrin, a significant iron transport protein in humans. Amino acids 1-331 form the N-terminal region, while amino acids 338–679 form the C-terminal domain. Every domain has the ability to bind one iron atom and a carbonate anion simultaneously [53].

There are studies that have found an increase in transferrin. Research has repeatedly demonstrated that people with type 2 diabetes have higher serum transferrin levels than people without the disease. For instance, transferrin was found to be positively correlated with incident type 2 diabetes in a Korean study, indicating the beginning of the disease in people who were not diabetic [54]. According to a different study, people who developed type 2 diabetes had a mean concentration of transferrin that was considerably higher than that of people who did not [55]. While researchers [56-58] believe the reason for this increase is: Oxidative stress and elevated iron reserves may be the source of elevated transferrin levels in individuals with type 2 diabetes. Studies demonstrate that increasing transferrin saturation is related with a higher risk of type 2 diabetes, demonstrating a relationship between iron metabolism and the disease. Elevated transferrin levels are a result of insulin resistance and poor glycemic control caused by iron overload and oxidative damage. Furthermore, type 2 diabetes is frequently associated with non-transferrin-bound iron (NTBI), which suggests further disruption of iron metabolism. Iron excess is more strongly linked to insulin resistance in type 2 diabetes patients, which results in increased transferrin saturation [59]. People with diabetes have increased transferrin saturation because iron excess has been linked to the development of the disease and its symptoms [60]. Furthermore, there is mounting proof that iron overload and insulin resistance are related in people with type 2 diabetes, which may explain higher transferrin levels [61]. Moreover, diabetes in individuals with type 2 diabetes has been associated with elevated ferritin levels, suggesting a link between iron metabolism and diabetes [62].

On the other hand, the researchers found a decrease in transferrin (iron) saturation and attributed the reason for this to: low transferrin levels can be linked to oxidative stress and inflammation in type 2 diabetes. In type 2 diabetes, poor glycemic control and vascular dysfunction may be linked by iron-mediated oxidative stress [63].

TOTAL IRON-BINDING CAPACITY (TIBC) AND TYPE 2 DIABETES

Total iron-binding capacity (TIBC) is a measurement of the total quantity of iron that blood proteins are capable of binding. This lab test aids in assessing the body's capacity to bind and move iron through the blood [64]. Transferrin is a blood protein that transports iron, and TIBC measures it indirectly. While low levels may signal iron overload, high TIBC levels may indicate iron deficiency. In order to determine the iron status and identify diseases like anemia and iron overload, TIBC is frequently used in conjunction with other tests, such as serum iron [65]. To determine iron status and make diagnoses, such as iron deficiency anemia,

TIBC is frequently utilized. Research indicates that TIBC has a strong association with other TIBC assays and may be determined with accuracy utilizing automated techniques. However, when serum ferritin is available for the diagnosis of iron deficient anemia, TIBC might not be able to offer further information [66]. It's crucial to remember that transferrin saturation and TIBC are closely related and can, in some circumstances, be used to estimate serum ferritin levels. All things considered, TIBC is a useful method for determining iron status, particularly in groups where transferrin genetic variants exist [67].

All previous studies confirmed a decrease in Total Iron-Binding Capacity, and this is due to several reasons mentioned by the researchers, as researcher [68] the plasma of diabetes people has a considerably decreased iron-binding antioxidant capacity, leading to decreased TIBC, Transferrin concentration and glycation can decrease the iron-binding antioxidant capacity of apotransferrin, contributing to reduced TIBC. While researcher [69] Individuals with diabetes, particularly those with type 2 diabetes, are more likely to have enhanced transferrin saturation, which could cause TIBC to drop. Another researcher discovered that patients with impaired glucose homeostasis, such as those with type 2 diabetes and prediabetes, had lower TIBC values [70]. According to one study, patients with greater blood ferritin levels, a marker of iron overload, in those with type 2 diabetes had considerably lower TIBC [71]. Reactive oxygen species can be assembled by free iron in the body, which can result in diabetes problems mediated by oxidative stress. This oxidative stress could be a factor in changes to TIBC and iron metabolism [72]. Glycemic control is an important factor. Patients with type 2 diabetes who have inadequate glycemic control typically have changed iron levels. Serum iron levels may rise with worsening glycemic control, changing TIBC and other associated measures. Glycated hemoglobin (HbA1c) levels that are elevated are linked to this development [73]. Iron metabolism is influenced by thyroid hormones, and abnormal thyroid function such as high TSH and low FT3/FT4 may raise the chance of developing type 2 diabetes [74]. In conclusion, oxidative stress, glycemic management, iron overload, and liver function can all affect TIBC levels in T2DM patients. For these people, maintaining glycemic control and keeping an eye on iron levels are critical to general health.

CONCLUSION

We conclude from this review that there is ample evidence linking iron levels to type 2 diabetes mellitus (T2DM). T2DM risk is positively correlated with elevated ferritin and transferrin saturation, but negatively correlated with transferrin levels and iron. A causal link between elevated systemic iron status and the risk of type 2 diabetes is also supported by genetic research. The exact strength of these correlations is still unknown, though.

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DECLARATION OF CONFLICT

The authors state that none of their known financial conflicts or interpersonal connections might have had an impact on the work presented in this paper.

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