J. Multidiscip. Res. Healthcare. Vol. 9, No. 2 (2023), pp.67–74

CHITKARA

Journal of Multidisciplinary Research in Healthcare

Journal homepage: https://jmrh.chitkara.edu.in/

Iron and β-Cell Function: Implications for Diabetes Pathophysiology

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ARTICLE INFORMATION

Received: January 21, 2023
Revised: March 14, 2023
Accepted: March 22, 2023
Published Online: April 22, 2023

Keywords:
Iron, Diabetes, Haemoglo-bin, Oxygen, β-cells

ABSTRACT

Background: The intricate relationship between iron metabolism and diabetes mellitus has become a subject of increasing interest, with a growing body of evidence suggesting that iron plays a significant role in the pathophysiology of diabetes. Specifically, the impact of iron on β-cell function has emerged as a critical area of study. β-cells, located in the pancreatic islets of Langerhans, are responsible for insulin synthesis and secretion.

Purpose: Understanding how iron influences these vital cells is crucial for unraveling the complexities of diabetes development and progression.

Methods: This review synthesizes current literature on the interaction between iron and β-cell function, exploring the molecular and cellular mechanisms underlying this relationship. We conducted a systematic search of databases, including PubMed and Scopus, to identify relevant studies published up to the present date. Articles were selected based on their focus on iron homeostasis, β-cell function, and their implications for diabetes pathophysiology.

Results: Iron is an essential micronutrient that participates in various cellular processes, including energy metabolism and reactive oxygen species (ROS) regulation. In β-cells, iron is intricately involved in insulin synthesis, folding, and maturation. However, an imbalance in iron homeostasis can lead to oxidative stress, mitochondrial dysfunction, and impaired insulin secretion. The reviewed literature provides compelling evidence that alterations in iron levels can adversely affect β-cell function, contributing to the development and progression of diabetes. Excess iron has been associated with increased oxidative stress within β-cells, leading to damage and dysfunction. Furthermore, iron-induced ROS may activate inflammatory pathways, promoting β-cell apoptosis and insulin resistance in peripheral tissues. Conversely, iron deficiency may also impact β-cell health. Insufficient iron availability can compromise the efficiency of insulin synthesis and secretion, potentially contributing to glucose dysregulation. Iron-deficient conditions may lead to alterations in cellular energy metabolism, further exacerbating the vulnerability of β-cells to stressors.

Conclusions: Understanding the nuanced interplay between iron and β-cell function has implications for diabetes management. Therapeutic strategies aimed at modulating iron levels, such as iron chelation or dietary interventions, hold promise for preserving β-cell health and improving glycemic control. This review underscores the intricate relationship between iron and β-cell function, providing valuable insights into the pathophysiology of diabetes. Whether through excess or deficiency, iron significantly influences the health and function of β-cells, shaping the landscape of diabetes development. Further research is warranted to delineate the precise mechanisms involved and to explore targeted interventions that may harness the therapeutic potential of modulating iron levels in diabetes management.

DOI: 10.15415/jmrh.2023.92007

1. Introduction

Diabetes mellitus, a complex and pervasive metabolic disorder, poses an ever-growing challenge to global public health. Its multifactorial nature, encompassing genetic predisposition, lifestyle factors, and intricate molecular mechanisms, necessitates a continual exploration of the intricate web of interactions that contribute to its pathophysiology. In recent years, the intersection between iron metabolism and diabetes has emerged as a focal point of investigation, unveiling a dynamic interplay that extends beyond conventional glycemic control (Prabhakar, 2020; Prabhakar *et al.*, 2020). This paper delves into the intricate relationship between iron and β-cell function, unraveling the implications for the pathophysiology of diabetes. Type 2 diabetes represents a prevalent and escalating global

ISSN No.: 2393-8536 (Print) ISSN No.: 2393-8544 (Online) Registration No. : CHAENG/2014/57978

health challenge. According to the International Diabetes Federation, currently world has 537 million diabetic population which is expected to reach 784 million by 2045. While its characteristic features, namely insulin resistance and β-cell dysfunction, are well-documented, the immediate triggers leading to type 2 diabetes and the intricacies of its genetic susceptibility remain considerably enigmatic. Various hypotheses have been posited, highlighting potential pivotal roles for anomalies in insulin signaling, insulin secretion, activation of stress pathways, mitochondrial dysfunction, hepatic fuel homeostasis, and central nervous system regulation (Lowell *et al.*, 2005). Despite these insights, the exact mechanisms driving type 2 diabetes persist as a scientific frontier.

Obesity is acknowledged as the most robust predictor of type 2 diabetes, directing significant attention to the interplay between nutrients and chronic caloric excess. While prevailing interest focuses on macronutrients, the significance of a micronutrient, iron, is underscored by its close association with diabetes risk in various hereditary syndromes and common forms of type 2 diabetes. Intriguingly, iron deficiency also exhibits an association with obesity. This review aims to succinctly outline the regulation of iron homeostasis at both organismal and cellular levels. Additionally, it will meticulously examine evidence indicating that elevated iron levels are linked to heightened diabetes risk, establishing a causal relationship. Furthermore, the review will shed light on how excess iron, even within the ostensibly "normal" range, exerts detrimental effects on critical aspects such as insulin secretion, insulin sensitivity, adipokine levels, and metabolic flexibility. Finally, we will delve into the molecular underpinnings of these intricate relationships.

In essence, this comprehensive exploration seeks to unravel the complex interplay between iron and the multifaceted landscape of type 2 diabetes, offering insights into both its etiology and progression. The review synthesizes existing knowledge and presents a compelling case for considering iron as a significant player in the intricate web of factors contributing to the development and manifestations of type 2 diabetes.

2. Regulation of Iron in Human Body

Iron serves as an indispensable cofactor for crucial processes such as fuel oxidation and electron transport. However, its potential to induce oxidative damage necessitates meticulous regulation, chaperoning, and, in cases of excess, sequestration. Consequently, intricate mechanisms have evolved to govern the uptake and destiny of iron. The nexus between iron and metabolism is well-established, particularly in lower organisms. In Saccharomyces cerevisiae, iron entry into cells escalates when required for fuel oxidation, a process signaled by Snf1 kinase, the yeast counterpart of AMP-dependent kinase (AMPK), in response to both glucose exhaustion and iron limitation (Haurie *et al.*, 2003). This intricate regulation extends to chromatin remodeling, as seen in the SWI/SNF complex controlling the induction of iron transport genes in S. pombe (Monahan *et al.*, 2008). Hence, the shift from fermentative to respiratory glucose metabolism prompts the stimulation of iron uptake to metallate enzymes and electron carriers pivotal for oxidative metabolism. The highly regulated nature of iron metabolism has been extensively reviewed (Hentze *et al.*, 2010), and this summary provides a current overview of ongoing explorations into mechanisms and pathways. Due to space constraints, intricate details and controversies are not exhaustively presented. In mammals, a considerable portion of iron, approximately 20–25 mg/day, is recycled through the erythroid pool as macrophages endocytose aging erythrocytes, with only 5–10% of this amount taken up through the intestine daily. Unlike some organisms, mammals lack a regulated mechanism for secreting excess iron. Equilibrium is maintained by losses through processes such as sloughing of the intestinal epithelium, cellular death, and biliary excretion, but when uptake surpasses these losses, excess iron is sequestered intracellularly.

Owing to the relatively slow disposal of excess iron in humans, the uptake of iron from the intestine is tightly regulated. In the duodenum, ferric (Fe^{3+}) iron undergoes initial reduction to ferrous iron (Fe^{2+}) facilitated by the ferrireductase duodenal cytochrome b (DCTB). Subsequently, ferrous ions enter the cell via the divalent metal-ion transporter 1 (DMT1 or SLC11A2). The exit of iron from the enterocyte is facilitated by ferroportin (FPN or SLC40A1), the sole known iron export channel. Once in circulation, iron is oxidized to Fe3+ by hephaestin (HEPH) and binds to transferrin. Cells can then uptake transferrin-bound iron through transferrin receptors (TfR), with TfR1 being prevalent in most cells. A soluble form of the transferrin receptor bound to transferrin also exists, and its serum levels act as a sensitive indicator of functional iron deficiency (Beguin, 2003). TfR1 facilitates iron uptake in a multitude of cells. Upon endocytosis, the endosome undergoes acidification, releasing ferric iron from transferrin. This iron is subsequently reduced by the STEAP family of ferrireductases before entering the cytosol through DMT1, though alternative transporters, such as Zip14, may also contribute. Non-transferrin-bound iron can directly enter cells through DMT1 and other transporters, especially under conditions of iron overload when transferrin approaches saturation. The majority of iron is directed to the mitochondrion for heme and iron-sulfur cluster synthesis, although the intricacies of its trafficking for these purposes are

not fully elucidated. Cytosolic iron levels are autoregulated via binding to Iron Regulatory Proteins (IRP). Excess iron releases IRPs from the iron responsive element (IRE) on the 3′-UTR of the TFR1 mRNA and the 5′-UTR of the ferritin mRNA, as well as the UTRs of various other iron-regulated proteins. Consequently, this results in decreased TfR mRNA stability, curbing further iron uptake, and augmented ferritin translation. A proportion of the increased ferritin is secreted, predominantly iron-free, serving as an indicator of tissue iron stores.

Transferrin-bound iron engages with hepatocyte TfR2 and the protein HFE on hepatocyte surfaces. This interaction, involving hemojuvelin (HJV), bone morphogenic protein (BMP)-6, and the SMAD pathway, stimulates hepcidin production, a regulatory peptide pivotal in human iron homeostasis. Human mutations affecting TfR2, HJV, HFE, and hepcidin result in iron overload, underscoring their significance. Hepcidin, upon entering the systemic circulation, induces the internalization and degradation of ferroportin in intestinal epithelial cells, acting as a negative feedback regulator of iron absorption. Hepcidin also regulates iron efflux from other cells expressing high ferroportin levels, such as macrophages. Although iron exit from the enterocyte primarily controls body iron entry, DMT1 is also subject to regulation by iron- and potentially hepcidin-dependent mechanisms, as well as by the hypoxia-inducible transcription factor HIF-2α (D'Alessio *et al.*, 2012). Additionally, dietary heme is directly absorbed by enterocytes through less well-defined pathways, facilitated by heme oxygenase (HMOX), which releases iron from heme (Hentze *et al.*, 2010; Beguin, 2003).

When evaluating the metabolic effects of iron, it is crucial to consider the remarkably wide "normal" range of serum ferritin in humans, varying from 30–300 ng/mL in men to 15–200 ng/mL in women. This 10-fold normal variation raises questions about the ideal definition of "normal." Despite meticulous regulation of iron uptake, dietary iron excess can lead to tissue iron levels surpassing those required for normal erythropoiesis and metabolic function. Many standard rodent chows, for instance, vary more than tenfold in iron content. Iron bioavailability is a key consideration, and when all factors are taken into account, several normal diets deliver significantly higher iron amounts than those consumed by wild mice or required for maintaining normal breeding and hemoglobin concentrations. This suggests that the broad range of "normal" iron levels may encompass concentrations posing health risks that are currently not fully understood. Iron homeostatic pathways are intricately connected to inflammatory stressors. Inflammation substantially upregulates hepcidin, mainly through IL-6, leading to significant increases in serum ferritin levels (Ganz & Nemeth, 2009). The suppression of intestinal iron uptake during inflammation has been theorized to be related to the beneficial sequestration of iron from invading microbes. This phenomenon may also provide insights into the link between iron and diabetes, a condition closely associated with inflammation. The relationships among diabetes, inflammation, and ferritin are complex, with ferritin potentially reflecting either excess iron stores causing diabetes, inflammation-causing diabetes, or both. If iron contributes to diabetes, one plausible mechanism involves its ability to induce oxidative stress, potentially linked to inflammation (Ganz & Nemeth, 2009). The subsequent sections will delve into evidence suggesting that iron overload alone is sufficient to induce diabetes.

3. β-cell Failure and Insulin Sensitivity

The initial and most evident indications of a correlation between iron levels and human diabetes emerged through clinical observations of individuals with pathological iron overload. This encompassed instances of hereditary hemochromatosis (HH) (Moirand *et al.*, 1997), as well as cases of transfusional iron overload (Dmochowski *et al.*, 1993). The most extensively studied illustration of the latter is β-thalassemia major, although diabetes also arises as a complication in other conditions necessitating frequent or prolonged transfusions, such as bone marrow transplantation (Baker *et al.*, 2005). Certain uncommon causes of diabetes, like Friedreich ataxia, are also linked to disruptions in iron balance and mutations in proteins that regulate iron metabolism (Radisky *et al.*, 1999). Herein, we elaborate on the characteristics of these conditions associated with iron overload. Hereditary hemochromatosis (HH) is inherited as an autosomal recessive trait and is found in approximately five per thousand Caucasians of Northern European descent (Pietrangelo, 2010). Most HH patients carry a homozygous mutation in the HFE gene, resulting in the C282Y substitution in the HFE protein (Feder *et al.*, 1996). Mutations in TfR2, HJV, and hepcidin are rarer causes of hemochromatosis (Pietrangelo, 2010). Normal HFE is partially necessary for iron stimulation of hepcidin, and in the absence of HFE protein, hepcidin expression decreases, leading to inappropriately high iron absorption given the body's iron load. The high prevalence of HFE mutations suggests a potential adaptive function, preventing iron uptake restriction in populations evolving without consistent access to dietary iron. HH, initially described as a triad of diabetes, cirrhosis, and skin pigmentation, has a prevalence of diabetes ranging from 7% to 40% in smaller clinical studies. However, unbiased screens for diabetes prevalence, taking into account the genetic cause of HH, reveal a prevalence of diabetes around 13–22% and impaired glucose tolerance at 18–30%. HH primarily

affects individuals of Northern European descent, where the baseline diabetes prevalence is approximately 5–10%. Some studies have not found an increased prevalence of diabetes in C282Y homozygotes, though the inclusion of homozygotes in a control population of mixed racial/ethnic descent may have skewed the baseline diabetes prevalence.

The pathophysiology of diabetes associated with HH remains controversial, with evidence suggesting contributions from both insulin deficiency and insulin resistance. Studies on this subject are challenging to interpret since they often involve subjects with established diabetes, where hyperglycemia itself may result in insulin resistance and insulin secretory abnormalities (Rossetti *et al.*, 1990). In a study focusing on HH subjects with prediabetes, the findings indicated significant differences from controls only in terms of insulin secretory capacity, with a trend toward increased insulin sensitivity (McClain *et al.*, 2006). Individuals with overt diabetes in HH exhibit insulin resistance, but the majority of them (80%) are also obese. These data suggest that HH itself is diabetogenic primarily due to decreased insulin secretion, and diabetes usually occurs when an independent mechanism, such as obesity, introduces insulin resistance. HH individuals cannot respond with increased insulin secretion due to primary pathology in the β-cells, making them highly prone to diabetes development when insulin resistant (McClain *et al.*, 2006). Consistent with this hypothesis, insulin secretory abnormalities, but not insulin sensitivity, improve when individuals with HH undergo phlebotomy (Hatunic *et al.*, 2010). β-thalassemia major and transfusional iron overload Thalassemia is a group of disorders characterized by deficient production of the β-globin subunit of haemoglobin (Weatherall, 1998). Patients with thalassemia become iron overloaded due to numerous transfusions required to maintain adequate erythrocyte levels and increased iron absorption (Weatherall, 1998). A single unit of blood contains up to 100 times the amount of iron that enters the circulation daily through the gut. The prevalence of diabetes in patients with thalassemia is 6–14%. Several studies have shown that both insulin resistance and insulin deficiency characterize both the prediabetic state and diabetes in thalassemia. However, insulin secretory defects may appear earlier than

4. Diabetes and Dietary Iron

Elevated iron stores are also linked to the onset of typical type 2 diabetes, as extensively discussed by (Fernández-Real *et al.*, 2008). A case in point is a study involving 9,486 U.S. adults as part of the National Health and Nutrition Education Survey (NHANES), revealing odds ratios for newly diagnosed diabetes of 4.94 for men and 3.61 for women with elevated serum ferritin levels (Ford & Cogswell, 1999). This iron-related risk is comparable to the relative risk associated with obesity. Similar associations between iron and diabetes risk or insulin resistance have been observed in diverse populations, including Europeans, African-Americans, as well as in conditions such as gestational diabetes (Afkhami-Ardekani & Rashidi, 2009) and pre-diabetes (Sharifi *et al.*, 2008). Recent NHANES data further indicates that elevated ferritin roughly doubles the risk for metabolic syndrome, independent of factors like age, race, alcohol, smoking, and inflammatory state measured by C-reactive protein (CRP) levels. High ferritin is also positively correlated with central adiposity, hepatic steatohepatitis, and cardiovascular disease. Given that type 2 diabetes involves chronic inflammation, and ferritin levels rise with inflammation, the question arises: does high iron, indicated by high ferritin, cause diabetes, or does diabetes lead to elevated ferritin levels? Several lines of evidence support the former causality. In the aforementioned study on metabolic syndrome, markers of inflammatory stress, such as CRP, did not explain the association of ferritin with diabetes. Other studies have similarly concluded that the diabetes risk linked to high iron is not attributable to hereditary hemochromatosis (HH) or inflammation but is rather related to dietary iron overload (Fleming *et al.*, 2001). Recent investigations into gestational diabetes have identified an increased risk associated specifically with dietary heme iron, which is more efficiently absorbed than non-heme iron (Qiu *et al.*, 2011). The most compelling evidence for the causality of iron, however, comes from studies in which the reversal of diabetes occurs with iron reduction.

5. Suppressed Iron Load as a Tool for Diabetes Management

The preceding data suggest that reducing iron stores in the context of dietary iron excess can have a dual positive impact on diabetes risk, enhancing both insulin secretion, as observed in studies of hereditary hemochromatosis (HH), and insulin sensitivity through mechanisms that include increased adiponectin. The β-cells are expected to exhibit a similar response and susceptibility to iron overload in both HH and dietary overload due to low or absent ferroportin (Hudson *et al.*, 2010). Additionally, β-cells may be particularly responsive to iron due to the high expression of DMT1 (Koch *et al.*, 2003), necessary for importing zinc for secretory packaging but also capable of transporting free serum iron, levels of which rise as transferrin approaches higher iron saturation levels. The favorable effects of phlebotomy have been demonstrated in various animal

models of type 2 diabetes. Otsuka Long-Evans Tokushima Fatty (OLETF) rats subjected to phlebotomy or fed an iron-deficient diet exhibit lower hemoglobin A1c levels compared to controls. Similar outcomes are observed in the leptin-deficient Ob/Ob model of type 2 diabetes, where low iron diets or iron chelators provide significant protection from diabetes, attributed to both increased insulin secretion and sensitivity. Notably, these effects of lowering iron are long-lasting and reversible, and importantly, they occur with levels of iron restriction that do not result in iron-deficiency anemia. Consistent with these findings, iron-deficient veal calves and rats display greater insulin sensitivity than iron-sufficient controls and show increased glucose utilization (Hostettler-Allen *et al.*, 2003).

Surprisingly, human data on the effects of iron depletion in common type 2 diabetes are limited. In relatively small and short-term studies involving non-HH subjects with or without known type 2 diabetes, phlebotomy improves insulin sensitivity, insulin secretion, and glycemia. Blood donors also show increased insulin sensitivity and secretion, although there may be selection bias in these studies concerning the population that donates blood. The study on the relationship between iron and adiponectin, summarized in the previous section, also included a proof-of-concept study involving a very small sample of prediabetic humans, where phlebotomy was performed to bring individuals from the highest quartile of normal ferritin down to the lowest quartile (Gabrielsen *et al.*, 2012). This intervention improved adiponectin, the area under the glucose curve, and the insulin disposition index, which represents the product of insulin secretion and insulin sensitivity and serves as a useful predictor of diabetes risk.

6. Molecular Mechanisms for Iron Regulation of Glucose Metabolism

Possible molecular pathways for iron's influence on the regulation of glucose metabolism are being explored. These mechanisms involve intricate processes within cells and encompass a range of effects, from reactive oxygen species generation to the modulation of hypoxia-inducible factors, AMP-activated protein kinase activation, and iron-responsive elements' impact (Figure 1). Additionally, epigenetic modifications influenced by iron, such as histone deacetylation and histone demethylation, may play roles in shaping glucose metabolism. These pathways highlight the complex interplay between iron levels and cellular processes related to glucose regulation.

Exploring the potential molecular mechanisms underlying iron regulation of glucose metabolism is an area where understanding is still in its early stages. Given the myriad effects observed in various tissues and the involvement of iron in processes such as glucose and fat oxidation, hypoxia sensing, CO and NO sensing, transcriptional regulation, generation of reactive oxygen species, and hormone level regulation, the impact of iron is likely to be diverse. Moreover, these effects are expected to have distinct dose thresholds, varying across the spectrum from iron deficiency to the broad range of normal to iron excess.

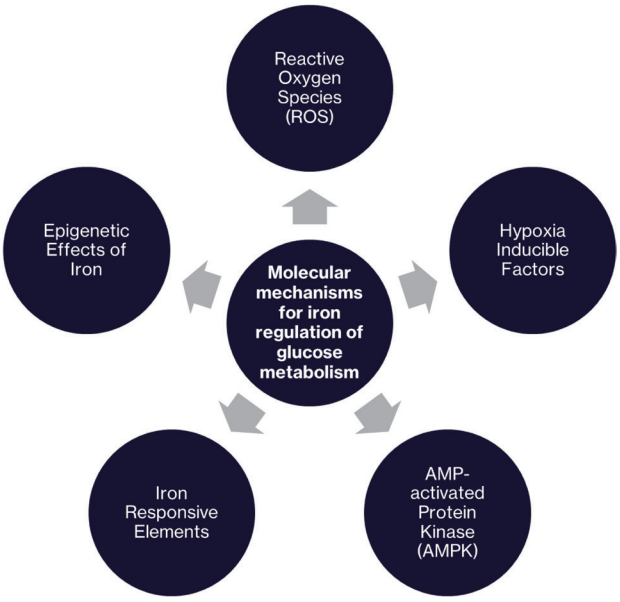

Figure 1: The process through which iron-induced glucose homeostasis works

6.1. Reactive Oxygen Species (ROS)

Iron has the capacity to generate hydroxyl radicals from peroxide and can hinder antioxidant defences like SOD2. While iron deficiency is also associated with increased ROS, elevated iron levels have been linked to oxidative damage implicated in cardiovascular disease, diabetes, atherosclerosis, and neurological degeneration. In diabetes progression, ROS can contribute to both β-cell failure and insulin resistance. β-cells, due to low expression of antioxidants, are particularly susceptible to ROS. The impact of ROS on β-cell dysfunction includes reduced insulin gene expression and direct modification of circulating human insulin, affecting its receptor binding. ROS can also induce insulin resistance through mechanisms such as FOXO1 activation (Jomova & Valko, 2011).

6.2. Hypoxia Inducible Factors

HIF-1 and -2 regulate cellular responses to low oxygen levels and play roles in angiogenesis, erythropoiesis, and glycolytic flux. These factors also influence iron metabolism,

with HIF-2 upregulating DMT-1 and DCYTB under low iron conditions, and HIF-1 decreasing ferritin. Conversely, cellular iron levels regulate HIF protein levels through prolyl hydroxylase (PHD) activity. Conditions of low iron or low oxygen stabilize HIF by inhibiting PHDs, impacting glucose sensing and insulin secretion in β-cells (Semenza, 2012).

6.3. AMP-activated Protein Kinase (AMPK)

AMPK, sensing cellular energy status through the AMP to ATP ratio, regulates energy balance. Iron can activate AMPK independently of adiponectin, potentially through alterations in AMP/ATP ratios caused by iron-induced mitochondrial dysfunction or stimulation of upstream activating kinase LKB1 by SIRT1-mediated deacetylation. The activation of AMPK by iron generally has antidiabetic effects on glucose disposal, gluconeogenesis, and lipid oxidation (Haurie *et al.*, 2003; Hardie, 2011).

6.4. Iron Responsive Elements

IRPs play a crucial role in maintaining cellular iron homeostasis by binding to iron responsive elements (IREs). IRP1 functions both as an iron sensor and as a cytosolic aconitase when bound to iron sulfur clusters. This dual role extends to controlling mitochondrial and cytosolic citrate levels. Abnormal IRP1 activity is observed in Friedreich ataxia, a condition associated with an increased prevalence of type 2 diabetes (Hardie, 2011).

6.5. Epigenetic Effects of Iron

Maternal iron intake impacts the metabolic programming of offspring, and there is evidence suggesting that iron controls epigenetic modifications. Iron may influence histone deacetylases, such as the sirtuin family, and histone demethylases, like Jumonji C-domain-containing demethylases. The co-regulation of iron levels and metabolic parameters is conserved across various organisms. It's worth noting that the mentioned mechanisms do not encompass all potential pathways through which iron may contribute to diabetes risk. Additional factors like heme, mitoNEET, and various cellular processes requiring heme or iron sulfur clusters further highlight the intricate and complex relationship between iron and metabolism, emphasizing the need for continued research in this area (Anderson *et al.*, 2012).

7. Summary

Observations in human populations and experiments with animals have firmly established a correlation between the amount of iron stored in tissues and the risk of diabetes. Some of these studies suggest a causal relationship, indicating that elevated iron levels alone can lead to diabetes. However, it is essential to recognize that iron exerts a range of effects in various tissues, which can either promote or inhibit diabetes across the spectrum from iron deficiency to excess. In the β-cell, for instance, excessive iron proves harmful, yet there is a clear necessity for a minimum iron level to ensure the proper function of proteins involved in glucose oxidation and sensing. While iron overload is linked to diabetes risk, iron deficiency is associated with another significant diabetes risk factor-obesity. However, the phenotypes of iron excess and obesity are not mutually exclusive. It is conceivable that the combination of obesity and iron overload may be particularly predisposed to causing diabetes due to a combination of insulin deficiency and resistance. Furthermore, the manifestation of these effects likely depends on a complex interplay of environmental and genetic factors.

8. Competing Interests

The authors declares that there is no conflict of interest

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Journal of Multidisciplinary Research in Healthcare

Chitkara University, Saraswati Kendra, SCO 160-161, Sector 9-C, Chandigarh, 160009, India

Volume 9, Issue 2 **April 2023** **ISSN 2393-8536**