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IMPACT OF IRON HOMEOSTASIS ON INSULIN RESISTANCE IN DIABETIC PATIENTS

Laboratory Medicine

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ABSTRACT

Maintaining iron levels in the body, known as iron homeostasis, is crucial in various biological processes. The perturbation of this equilibrium, particularly in the presence of excessive iron, can impact metabolic pathways and exacerbate insulin resistance. The objective of this investigation is to examine the association between iron homeostasis and insulin resistance among individuals who have been diagnosed with diabetes or prediabetes. The study findings revealed that the test group exhibited notably increased l fasting and postprandial blood glucose levels, Hemoglobin A1C, insulin, and Homeostasis Model Assessment of Insulin Resistance values, indicative of compromised glucose regulation and insulin resistance. Significantly, the test group demonstrated elevated ferritin levels, indicating augmented iron reserves, which could be linked to insulin resistance. The findings of this study highlight a plausible association between perturbed regulation of iron levels and impaired insulin sensitivity among individuals with diabetes. Additional investigation is imperative to elucidate the intricacies of this correlation and its ramifications for strategies aimed at preventing and treating diabetes.

KEYWORDS

Diabetes, Iron, Insulin resistance, Diabetes mellitus, reactive oxygen species, Oxidative stress, Nutritional deficiency

INTRODUCTION

Iron homeostasis pertains to maintaining iron concentration in the body, which is essential for facilitating vital biological processes such as DNA synthesis, oxygen transport, and energy production[1]. The regulation of iron levels is crucial to prevent toxicity that may arise from excessive iron accumulation. The intricate equilibrium is upheld by a multifaceted system of proteins and pathways that govern the processes of iron absorption, transportation, storage, and utilization.

Iron homeostasis has garnered increasing attention in the study of metabolic disorders such as diabetes in recent times[2]. It is worth noting that there exists a growing body of evidence indicating that the disturbance of iron homeostasis may play a role in the onset of insulin resistance, which is a significant pathological characteristic of type 2 diabetes. To begin with, an overabundance of iron can trigger the production of detrimental reactive oxygen species (ROS) through Fenton chemistry. Reactive oxygen species have the potential to cause harm to a variety of cellular constituents, such as proteins, lipids, and DNA[3]. Within the framework of insulin resistance, oxidative stress-induced harm can hinder insulin signaling pathways across a range of tissues, with particular emphasis on the liver, muscle, and adipose tissue.

Furthermore, heightened levels of iron can impede the insulin signaling pathway[4]. The excessive accumulation of iron can interfere with the proper functioning of insulin receptor substrates (IRS), which are essential proteins in facilitating the actions of insulin[5]. Insulin resistance can occur, which may impede the body's capacity to react to insulin effectively[6]. The hormone hepcidin, essential in regulating iron balance within the body, has been linked to the development of insulin resistance. The regulation of iron release from cells, including adipose tissue, is governed by hepcidin. Studies have shown that individuals who exhibit insulin resistance frequently display heightened concentrations of hepcidin, resulting in the intracellular accumulation of iron and the exacerbation of insulin resistance.

On the other hand, it is noteworthy that iron homeostasis can be impacted by insulin resistance and the systemic inflammation that is frequently linked to it. The inflammation process can trigger the synthesis of hepcidin, which can cause alterations in the transportation and retention of iron[7]. These changes have the potential to create a loop of insulin resistance. In general, the intricate and incompletely comprehended association between iron homeostasis and insulin resistance underscores that disturbances in iron regulation may play a role in the development of diabetes. This nascent comprehension unveils prospective novel pathways for prevention and therapy, albeit further investigation is required to capitalize on these prospects optimally.

MATERIALS AND METHODS

A comparative cross-sectional study was conducted on patients with a prior diagnosis of type 2 diabetes mellitus who were undergoing treatment at the diabetic clinic located at the Sevana clinic in Kozhikode, Kerala. The examination's temporal coverage encompasses December 2020 to May 2022. The study's inclusion criteria stipulated that participants must be 35 to 65 years old, express a willingness to participate, and not have any life-threatening illnesses such as liver disease, renal disease, endocrine disease, or cancer. Every individual was matched with a counterpart of the same age and gender. The initial study aimed to select control participants aged 35 to 65 and exhibiting no clinically severe symptoms. Demographic information, baseline lipid profile values, and biochemical markers were collected and documented on the Datasheet. Following the venepuncture procedure, a 5 ml blood sample was obtained and processed using standard techniques to separate the serum.

Biochemical parameters such as fasting blood sugar, transferrin, ferritin, and TIBC are measured.

The researchers employed diverse and suitable statistical techniques to evaluate the parameters. The study used descriptive statistics to assess demographic variables, including age, gender, height, and body mass. The study employed the Pearson correlation test to assess the association between iron homeostasis and insulin resistance. The statistical analysis was performed utilizing the SPSS software.

RESULTS AND DISCUSSION

To assess the regulation of iron levels within the body, transferrin, ferritin, and TIBC levels are quantified through serum analysis. The statistical significance of the data was assessed by utilizing SPSS version 20. The results were statistically significant at or below the 0.05 level. The collected data is subjected to statistical analysis, wherein the mean is computed, and the standard deviation is calculated and subjected to statistical testing. The experimental group exhibited a statistically significant increase in body mass index (BMI) compared to the control group. The experimental cohort showed significantly higher fasting blood glucose, postprandial blood glucose, and hemoglobin A1c levels than the control cohort. The test group exhibits significantly elevated levels of ferritin and TIBC, whereas the control group displays considerably reduced transferrin levels. Studies have demonstrated an association between elevated ferritin levels and type 2 diabetes and premature irregularities in glucose metabolism. This topic has been the focus of most prior investigations on the relationship between iron status and T2DM. Following the aforementioned discoveries, after adjusting for various plausible extraneous variables, our findings regarding ferritin indicate that the perceived intensity of the correlation is nearly identical amongst individuals with T2DM and is more robust in individuals who have recently been diagnosed with diabetes as opposed to those who have been previously diagnosed, implying that ferritin, or heightened bodily iron levels, may be implicated in the initial development of T2DM. Our study revealed a positive correlation between elevated ferritin levels and fasting hyperglycemia. There is a need for increased emphasis on transferrin. The findings indicate an inverse association between ferritin levels and

transferrin production, as an elevation in the latter, accompanies a decline in the former. Our study revealed a robust association between elevated transferrin levels and the incidence of type 2 diabetes.

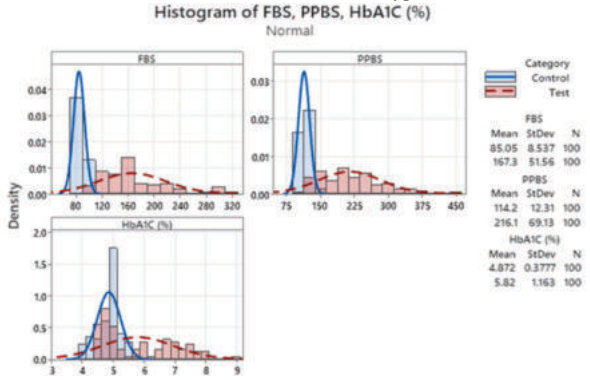

Figure 1: An analysis of glycemic parameters in the control and experimental groups.

Table 1: Comparison of parameters between the control and test subjects for insulin level and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), calculated using insulin and FBS.

Parameters	Category		t-test	p-value
	Control (n=100)	Test (n=100)		
INSULIN	8.72 ± 11.29	15 ± 10.21	-4.12	<0.01**
HOMA IR	1.84 ± 2.4	6.11 ± 4.7	-8.09	<0.01**
All values are mean ± standard deviation, n: Number of subjects, LBW: Low Birth Weight, NBW: Normal Birth Weight. The statistical test used is the t-test. *Significant at p<0.05, **significant at p<0.01.				

The t-test results indicate that the control group exhibited significantly lower insulin levels and HOMA IR values in comparison to the test group. The statistical significance of the observed differences in both cases is confirmed by the p-value being less than 0.01, indicating a 99% confidence level.

To summarize, the table 1 indicates that the test group exhibited markedly elevated insulin levels and HOMA IR values in comparison to the control group. The table lacks information pertaining to the characteristics of the groups in question. However, the elevated insulin and HOMA IR values observed in the experimental group may suggest the presence of insulin resistance, potentially among individuals with diabetes or prediabetes.

Table 2: Correlation between serum ferritin and insulin resistance in patients with satisfactory glycemic control

Sample 1	Sample 2	N	Correlation	95% CI for ρ	P-Value
INSULIN_1	HOMA	200	0.848	(0.804, 0.883)	0.000
Ferritin ng/ml)	HOMA	200	0.424	(0.304, 0.532)	0.000
Ferritin ng/ml)	INSULIN_1	200	0.214	(0.077, 0.342)	0.002

Table 3: Descriptive Statistics: INSULIN_1, HOMA, Ferritin ng/ml)

Variable	Category	Mean	SD.
INSULIN_1	Control	8.72	11.29
	Test	15.00	10.21
HOMA	Control	1.837	2.403
	Test	6.108	4.703
Ferritin ng/ml)	Control	39.12	21.45
	Test	155.41	31.91

Regarding insulin levels, the experimental group exhibited a higher mean value of 15.00 with a standard deviation 10.21. In contrast, the control group demonstrated an average insulin level of 8.72 with a standard deviation of 11.29. The Homeostasis Model Assessment of Insulin Resistance (HOMA) values for the control group showed an average value of 1.837 and a standard deviation of 2.403. According to the results, the test group had a significantly higher mean HOMA value of 6.108 and a standard deviation of 4.703. These findings suggest that the test group may be experiencing a state of insulin resistance. The ferritin levels, a protein found in blood cells responsible for iron storage, were assessed in both cohorts. The experimental group exhibited a mean ferritin level of 39.12 ng/ml and a 21.45 ng/ml standard deviation. By way of comparison, it can be observed that the experimental cohort exhibited a significantly higher mean ferritin concentration of 155.41 ng/ml, accompanied by a standard deviation of 31.91 ng/ml. The observed rise in ferritin levels among the participants in the experimental group could indicate complications in iron metabolism or inflammation. The data indicates notable insulin, HOMA, and ferritin concentration variations between the control and experimental cohorts.

Declaration Of Interest

The authors state that they have no conflict of interest that may be seen as impairing the research's objectivity.

CONCLUSIONS

Preserving the intricate equilibrium of iron within the body, commonly called iron homeostasis, is paramount for various physiological processes. The disturbance of homeostasis, as observed in cases of excessive iron accumulation, can substantially influence metabolic pathways, including those involved in insulin signaling, potentially precipitating insulin resistance. The data presented indicates that the group denoted as the "test" group, presumably comprising individuals with diabetes or prediabetes, exhibits elevated fasting and postprandial blood glucose levels and increased HbA1C values compared to the "control" group. The findings illustrate an elevated blood glucose level over a prolonged period in the experimental cohort, suggesting compromised glucose homeostasis, a characteristic feature of insulin resistance and diabetes. The test group exhibited significantly elevated insulin levels and Homeostasis Model Assessment of Insulin Resistance (HOMA IR) values, further highlighting the presence of insulin resistance. Elevated insulin levels may serve as a compensatory mechanism in response to insulin resistance, whereby the organism generates more insulin to counteract the resistance. The higher HOMA IR values observed in the experimental cohort suggest a reduced responsiveness to the physiological actions of insulin, which aligns with the established concept of insulin resistance. Notably, the test group exhibited a significant elevation in ferritin levels. Ferritin, a protein in blood cells and containing iron, indicates iron reserves in the body and may also show heightened levels in reaction to inflammatory processes. Elevated levels of ferritin within the framework of iron homeostasis may indicate an augmentation in iron reserves and, conceivably, iron excess. Insulin resistance has been associated with an overabundance of iron in the body, which may be attributed to the production of detrimental reactive oxygen species that result in oxidative stress and impairment of the insulin signaling pathway. Furthermore, increased ferritin levels may suggest systemic inflammation linked to insulin resistance and diabetes. The results of this study provide a persuasive argument for the correlation between iron regulation and insulin resistance in individuals with diabetes. The available data support the hypothesis that altered iron regulation, as seen in elevated ferritin concentrations, may contribute to developing or escalating insulin resistance, a key pathological feature of type 2 diabetes. It is important to acknowledge that the correlation between iron homeostasis and insulin resistance is intricate and influenced by multiple factors. Further investigation is required to comprehensively comprehend this association and its ramifications for preventing and managing diabetes.

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