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Serum Ferritin Level Linked to Male Type-2 Diabetes Mellitus Patients Amongst Residents of Hyderabad, Sindh

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ABSTRACT

Introduction: Diabetes mellitus is a metabolic disorder which is caused by either deficiency of insulin or its disturbed action on peripheral receptors. Globally it is estimated that 451 million peoples were suffering from Diabetes mellitus type 2 in 2017 and this burden will rise to 693million in 2045.The relationship between diabetes mellitus and serum ferritin levels is intricately linked, sharing a common intersection in the liver where both glucose metabolism and iron metabolism converge.

Aims and Objectives: To measure the serum ferritin levels among residents of Hyderabad with type 2 Diabetes Mellitus.

Place and Duration of study: The study was conducted in the Outpatient Department (OPD) of Liaquat university Hospital from June 2022 to August 2022 (3 months).

Material and Methods: The study consists of 100 subjects divided into two groups, a control group consists of 50 normal healthy people with normal fasting glucose below 100mg/dl and a Case group consists of 50 patients with fasting glucose level more than 125 mg/dl according to World Health Organization criteria. Their Serum ferritin levels were evaluated using the ELFA method, employing a commercially available kit supplied by Roche Cobas Integra. The results were analyzed on the software Graph Pad Prism 9, p-value $\leq 0.05$was taken as significant.

Results: The frequency of Type 2 Diabetes mellitus was significantly higher in patients with increased serum ferritin levels (P=0.001) with an odds ratio of 1.838 , a sensitivity/specifity value of (0.50/0.56) and a robust likelihood ratio of 2.25.

Conclusion: The study underscores a potential link between elevated serum ferritin and Diabetes Mellitus Type-2.

Key Words: Diabetes Mellitus, Serum ferritin level, Association between two factors

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by dysregulation of insulin; a hormone responsible for regulating carbohydrate metabolism[1]. Diabetes mellitus comprises two primary types: Type-1, marked by inadequate insulin secretion from pancreatic beta cells; and Type-2, characterized by heightened peripheral resistance to insulin[2]. Iron stands as a vital micronutrient crucial for the human body, playing a pivotal role in various physiological processes.

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The absorption of iron takes place within the small pivotal role in various physiological processes. The absorption of iron takes place within the small intestine, and subsequently, it traverses the bloodstream to reach the iron-utilizing units within the body. It is noteworthy that in the circulatory system, iron is transported by a glycoprotein known as transferrin[3]. The iron overload leads to inflammation in the liver and pancreas. It decreases the insulin release and insulin resistance at the tissue level leading to Diabetes or deteriorating already existing disease[4]. The iron circulates in the plasma by binding to protein called transferrin which is regulated by a specific hormone called Hepcidin (HAMP). It is found that in Diabetes these hormones decrease in the serum leading to hyperferritinemia. The pathophysiology of this association involves increased iron accumulation in the body, which causes oxidative stress and damages hepatocytes. This affects the secretion of insulin and disrupts the normal regulation of glucose metabolism[5]. Elevated ferritin levels not only contribute to insulin resistance but also disturb cholesterol levels, increasing the risk of cardiovascular events such as atherosclerosis,

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arteriosclerosis, DVTs, metabolic syndromes, dyslipidemia, and even cancers[6]. Elevated serum ferritin levels in males are strongly associated with inflammation and oxidative stress, which play a critical role in the development of diabetes mellitus in the male population.[7] Males also tend to have more visceral fat and have higher glucose production in the liver than females, which leads to increased insulin resistance and a higher risk of developing diabetes mellitus in males.[8-9]. Ferritin, as one of the acute phase reactants, increases during inflammatory processes such as diabetes, which results from hepatocyte injury[10]. The normal levels of ferritin in blood serum vary from male to female with average level in 24 to 336 ng/ml in adult men and from 25 to 200 ng/ml in adult women[11]. An insightful meta-analysis underscores a discernible association, revealing heightened prevalence in the development of diabetes mellitus amongst individuals exhibiting elevated serum ferritin levels and abnormal Hepcidin levels, in contrast to those maintaining normative serum ferritin and Hepcidin levels[12]. Although inherited hemochromatosis and thalassemia were the pathologic disorders that initially revealed the connection between iron and diabetes, excessive dietary iron levels also increase the risk of Diabetes. Iron is directly and causally involved in the etiology of Diabetes, through its mediation of both insulin resistance and β-cell failure[13]. To mitigate the risk of diabetes mellitus, it is imperative to proactively manage lifestyle choices, maintain a well-balanced diet encompassing appropriate micro and macro nutrients, and utilize suitable therapeutic interventions. A pivotal aspect of this preventive approach involves vigilant monitoring and adjustment of ferritin levels to align with the established normal range[14]. Some other studies also shows that use of chelating agents also lowers chances of oxidative injury to insulin receptors and lowers the prevalence of Diabetes Mellitus Type-2[15]. The aim of this study is to investigate the serum ferritin levels amongst residents of Hyderabad with Type-2 Diabetes Mellitus. The rationale for the study is that, as this type of research has never been conducted in Hyderabad, Sindh, the findings will be included into guidelines for the management of diabetes mellitus in the local population.

MATERIAL AND METHODS

This comparative cross-sectional study was conducted from June 2022 to August 2022 after approval from Ethical Review Committee of Department of Physiology, Sindh University Jamshoro vide letter No Physiol/27, dated 10/03/2022. The venue was Outpatient Department of General Medicine in association with Research laboratory of Liaquat University Hospital Hyderabad. This study enrolled 100 male residents of District Hyderabad, Sindh. Male subjects were included due to differences in hematological parameters in males and females, and the hormonal influence of testosterone in males that affects the levels of serum ferritin compared to females. These confounding variables were considered for the accuracy of results, and only male subjects were included. The participants age ranged between 40 to 70 years. The control group consists of 50 normal healthy people with fasting glucose below 100mg/dl and Case group consisted of 50 patients with fasting glucose level more than 125 mg/dl. Only Diabetes Type 2 patients with a history of higher serum glycemic level (HbA1C level more than 6.5) for the last 2 years were selected. All those patients who were below 40 or more than 70 years, with history of blood transfusion, taking iron supplementation and having any chronic condition like hypertension were excluded from this study. The reluctant participants and those residing outside Hyderabad district are excluded.

The consent of all the participants was taken in written and they were completely briefed about the aims, objective and procedure of the study. A thorough clinical examination including blood pressure and pulse was recorded by digital sphygmomanometer. The fasting blood sugar level was monitored by Care Sense glucometer made in Korea. The blood samples of all the patients were subjected to analysis in order to quantify plasma glucose through glucose oxidase-peroxidase method. Whole blood specimens were collected in vials of EDTA and were employed for the determination of HbA1c through the Immuno-turbidimetric method. Serum ferritin levels were evaluated using the ELFA method, employing a commercially available kit supplied by Roche Cobas Integra.

Statistical Analysis:

The results were analyzed on the software Graph Pad Prism 9. Demographic data was analyzed by column option, while the Fischer's exact test was applied to deduce the *P*-value, which was considered significant at ≤ 0.05.

RESULTS

Age in DM2	Mean	Stdv	Std error of Mean	Min-Max	Lower 95% CI-Upper 95% CI
Age in DM2	54.28	7.10	1.01	43-66	7.01-7.40
Age in Non DM2	51.18	7.28	1.03	41-63	49.11-53.25
HA1C in DM2	7.20	0.69	0.09	6.5-9.0	7.0-7.40
HbA1c in Non DM2	5.34	0.64	0.09	4.3-6.4	5.16-5.52
BMI in DM2	22.72	2.11	0.29	18-26	22.12-23.32
BMI in Non DM2	18.85	.731	0.24	16.5-22.0	18.36-19.5
SF in DM2	340.3	15.40	2.17	303-359	335.69-344.6
SF in Non DM2DM2	247.4	17.36	2.45	204-270	242.5-252.3
FBS DM2	146	34.30	4.85	110-220	136.3-154.7
FBS in Non DM2	87.5	8.72	1.23	68-99	84-89.54

Table-1: Demographic Data of the Participants

Table-1 demonstrates the clinical and demographic value of participants. Only male patients with age group range between 41 to 66 years were selected. HbA1C (5.34 versus 7.20), serum ferritin (SF) (247.4 versus 340.3), BMI (18.85 versus 22.72) and fating blood sugar (87.5 versus 146) were on the higher level in Diabetic type 2 patients than non-Diabetic patients.

Status of patients	Increase serum ferritin	Normal serum ferritin	Total	*P-value*	*ODD Ratio*	*95 %CI*	*Sensitivity/ specifity*	*Like hood ratio*
Normal Patients n= 50	24(24%)	26 (26%)	50 (50 %)	0.001	1.838	1.2 to 2.3	0.50/ 0.56	2.25
Diabetic patients n=50	40(40%)	10 (10%)	50 (50 %)					
Total n=100	64(64%)	36 (36%)	100 (100%)					

Table-2: Association of serum ferritin level and Type-2 Diabetes mellitus

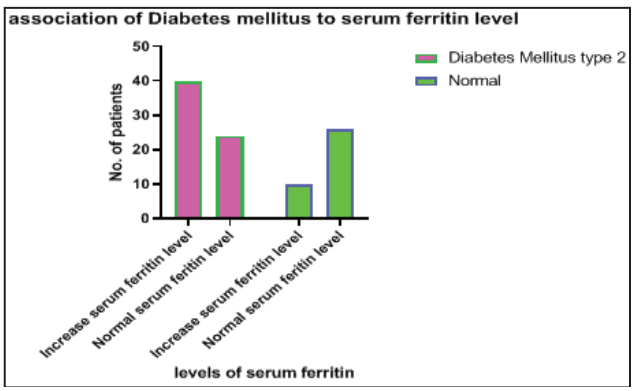

Fig-1: Association of serum ferritin level and Type-2 Diabetes mellitus (A Graphical Representation)

DISCUSSION

This study aimed to investigate the levels of serum ferritin levels in patients affected with Type-2 diabetes mellitus in residents of Hyderabad, Sindh, Pakistan. The results of this study show that among the sample size of 100 participants, raised serum ferritin level was present in 64 participants, with 40 people diagnosed with Type-2 Diabetes Mellitus and the remaining 24 being normal. These findings show that people with Type-2 Diabetes Mellitus are more likely to have high serum ferritin levels in comparison to the normal population. These findings are also supported statistically by a p-value of 0.001 and an odds ratio greater than 1, which proves that this relation of high serum ferritin in patients with Type-2 Diabetes Mellitus is statistically valid. These statistical findings are consistent with the results of Hossain et al., who conducted the same cross-sectional study in Bangladesh and found a significant relationship between serum ferritin levels and Type-2 DM[16]. Similarly, another systemic review and meta-analysis conducted by Wang et al. corroborated our study results by showing the presence of raised levels of serum ferritin in Type-2 DM in various populations[17]. Although the exact process is still unknown, research has suggested that the liver is a key player in this connection. This is further supported by research by R. Zhang et al. which discovered serum ferritin to be an independent risk factor for the onset of Diabetes Mellitus[18]. In addition; a recent study demonstrated that blood iron levels can be used to screen individuals at risk of developing diabetes mellitus. An increased serum ferritin level produces Diabetes Mellitus by decreasing insulin sensitivity at the receptor site and its release from the beta cells[19]. Furthermore, our statistical analysis provided robust evidence supporting the observed association. The calculated p-value of 0.001 shows that this relation is statistically significant, and these statistical measures also align with the results of the meta-analysis conducted by Chen et al., which shows the same results[20]. However, it is very important to acknowledge the opposite viewpoints present in different studies for the same relationship. A study conducted by Patel et al. and Kim et al. shows that there is no significant relationship between raised serum ferritin levels and the population affected by Type-2 Diabetes Mellitus[21,22]. Additionally, another study conducted by Li et al. and Shen et al. on Mendelian randomization also failed to find any causal or significant relationship between patients with Type-2 Diabetes Mellitus and altered serum

ferritin levels[23]. In conclusion, although there is compelling evidence linking blood ferritin levels to Type-2 Diabetes Mellitus, more investigation is required to clarify underlying mechanisms and effectively direct clinical practice. A multidisciplinary approach is needed to better understand and control this intricate interplay, integrating insights from clinical medicine, biochemistry, and genetics.

LIMITATIONS

There were some limitations to our study. Firstly, this is a cross-sectional study with a small sample size. Secondly, it includes only male patients not females . Thirdly this study was conducted in one institution, and consequently, the findings cannot be generalized to all regions.

CONCLUSION

This study underscores the relation between high serum ferritin level and frequency of Type-2.diabetes mellitus

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