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RESEARCH PAPER

The Gender-specific Association Between Serum Ferritin Levels and Insulin Resistance Markers in Bangladeshi Adults

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Abstract

Background: Recent research focused on iron stores' impact on diabetes, highlighting ferritin as a key biomarker. Studies revealed elevated ferritin, indicating increased iron stores linked with insulin resistance (IR). However, the connection between ferritin and IR exhibits variability based on ethnicity, gender, and glycemic state, leading to inconclusive findings. So, there is a notable gap in existing data regarding the relationship between ferritin and IR among South Asian men and women, especially in Bangladesh. To our knowledge, This is the first time we are evaluating the relationship between body iron stores and insulin resistance markers in our population.

Objectives: The aim was to examine the relationship between IR markers (fasting insulin, glucose, and HOMA-IR) and serum ferritin concentrations in Bangladeshi adults.

Methods: A cross-sectional analytical study was conducted at Sir Salimullah Medical College, Dhaka (March 2018 - February 2019). It involved 140 subjects aged 25-55. Among them, 92 were male and 48 were female. Multiple regression analysis was performed after determining ferritin levels, insulin levels, and fasting plasma glucose levels and calculating the homeostatic model assessment of IR (HOMA-IR in both genders after adjustment. Exclusion criteria were applied to eliminate individuals with inflammatory diseases, chronic conditions, major cardiovascular events, alcoholism, anemia, or specific medications that could affect ferritin levels.

Results: Females had lower mean ferritin ($p < 0.001$) than males. After adjustment for covariates in men-fasting glucose, insulin and HOMA-IR were significantly increased with increasing serum ferritin levels (P for trend < .001). The highest tertile is associated with older age, higher BMI, FPG, serum insulin, and HOMA-IR in men. In females, serum ferritin correlated positively only with FPG, not other markers.

Conclusion: In Bangladeshi adult men, serum ferritin concentrations were positively associated with fasting glucose, insulin, and HOMA-IR, indicating an essential role of iron storage in the pathogenesis of IR, while this association was not observed in women.

Keywords: Gender Differences, IR Markers, Serum Ferritin, adult population.

Introduction

In recent times, the health effects of having too much iron in the body have gained significant attention[1]. Growing evidence indicates that elevated levels of ferritin, a marker for iron stores in the body, are linked to the prevalence and risk of metabolic syndrome and type 2 diabetes. [2-4] Both metabolic syndrome and type 2 diabetes are multifactorial disorders closely related to insulin resistance (IR), making it likely that high ferritin levels are associated with IR. [4] Amid this escalating health crisis, the interplay between iron metabolism, specifically serum ferritin levels and insulin resistance (R), has emerged as a focal point of scientific inquiry, unveiling the potential link between abnormal iron storage and T2DM's pathogenesis.[5]

Iron, a vital micronutrient, is essential for enzymatic functions like oxidation and reduction[6]. Serum ferritin commonly indicates body iron status, influencing insulin resistance and beta cell dysfunction, key factors in glucose regulation.[7]

Some Observational studies have consistently shown that increased levels of circulating ferritin are

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associated with IR as measured by the homeostatic model assessment (HOMA) and reduced insulin sensitivity.[10,11] A few studies have demonstrated an association between markers of insulin resistance (fasting insulin, glucose, and HOMA-IR) and ferritin[2,8,9,12,13].

Research shows gender-specific differences in iron accumulation in muscles and its influence on glucose uptake vary across ethnicities and genders.[7,14-15] However, Robust studies on the sex-specific relationship between serum ferritin and diabetes are inconsistent. Additionally, diverse body compositions based on nationality may affect the association between serum ferritin and insulin resistance.[14]

Serum ferritin levels vary significantly between genders. Studies across diverse populations in Africa reveal that elevated ferritin levels correlate positively with Type 2 Diabetes Mellitus (T2DM) and fasting glucose, with this association notably stronger in women.[14] However, findings from Colombian and Finland studies show inconclusive results regarding ferritin's predictive role in insulin resistance (HOMA-IR) across the sexes.[16,17] Notably, research in Korea and Japan suggests a correlation between increased serum ferritin concentrations and insulin resistance and T2DM in men but not in women.[9,10] Conversely, a study in China found that elevated serum ferritin was associated with insulin resistance solely in diabetic women.[21] These findings highlight the nuanced relationship between ferritin, gender, and metabolic health. Most of these studies are conducted on Caucasian populations, with some conducted in Asian countries. Very few studies focused on the South Asian population, especially Bangladesh.

However, there is no published data regarding the gender exploration on the association of serum ferritin concentration with insulin resistance markers among the Bangladeshi adult population. A few studies explored the associations between elevated iron stores and metabolic disorders in Bangladeshi populations but did not show gender exploration.[23,24]

It identifies individuals with impaired fasting glucose who may benefit from interventions to prevent or delay the progression of Type 2 DM and its complications.[25] So, this study aims to explore the gender-specific relationship between serum ferritin and insulin resistance markers (fasting insulin, glucose, and HOMA-IR) in Bangladeshi adult subjects. If such a relationship exists, serum ferritin can serve as a predictor for screening for T2DM even before the disease manifests, identifying which gender is at high risk of developing the disease. Measures should be made to decrease serum ferritin levels, as it indicates the crucial role of iron storage in the pathogenesis of IR in Bangladeshi adult men.

Materials and Methods

An analytical cross-sectional study took place at the Department of Biochemistry, Sir Salimullah Medical College, Dhaka, Bangladesh, spanning from March 2018 to February 2019. This study enrolled a total of 140 participants. It focused on adults aged between 25 and 55 years. Among them, 92 were male and 48 were female. Participants with acute or chronic inflammatory diseases, chronic liver diseases, major cardiovascular events, chronic alcoholism, and anemia were excluded by history taking and clinical examinations. Conditions that altered ferritin level, e.g. Hemochromatosis, history of blood transfusion or iron therapy in the previous year, and subjects with very high serum ferritin level (>800 ng/ml) were excluded. History of taking antidiabetic, lipid-lowering agents, or other medication that affects carbohydrate, lipid, or insulin metabolism was also excluded. Those with malignancy and pregnancy were excluded. All surveys were conducted after obtaining written informed consent. Anthropometric variables were measured accordingly, and a blood sample was collected to measure biochemical variables.

Study Procedure: Subjects were selected from the outpatient Department of Medicine and Endocrinology. Sir Salimullah Medical College and Mitford Hospital, and a training center of Dhaka (NAEM) as routine examinations. Ethical permission was taken from the Ethical Review Committee of Sir Salimullah Medical College. Before collecting specimens, each eligible person was firmly approached and proper counseling about aims, objectives, and risks benefit and procedure of the study were done. Only voluntary candidates were recruited as participants. Then they were interviewed, and relevant information was recorded systematically in a pre-designed standard datasheet, including general information and history of chronic diseases, and family history of diabetes. Data were checked and edited. All surveys were conducted after obtaining written informed consent. Anthropometric variables were measured accordingly, and a blood sample was collected to measure biochemical variables.

Markers of insulin resistance as assessed by Fasting insulin, glucose, and HOMA-IR.[26]

Statistical Analysis: All statistical analysis was performed with the help of the software SPSS 22 (statistical package for social science). The mean with standard deviation was determined to compare continuous variables. Actual frequencies and percentages expressed categorical variables. An unpaired student's t-test was performed to show any significant difference between the mean values. ANOVA test was done to compare continuous variables. Serum ferritin concentrations were divided into tertiles to observe the trend of the related variables. Multiple linear regression analyses were performed to identify factors independently associated with HOMA-IR, plasma glucose, and serum insulin. $p < 0.05$ was considered a test of significance in all statistical tests. The sample size was determined by applying the formula for comparing two means. Using Ferritin values from Han et al.[27]

Results

This study investigated serum ferritin levels for their associations with various parameters in the adult population involving 140 subjects, including 92 males and 48 females. Ferritin concentrations were higher among men than women (98.72 ± 66.39 versus 36.20 ± 45.15,Â0.001) There are no significant differences in fasting glucose, insulin, and the homeostatic model assessment-insulin resistance (HOMA-IR) between men and women (Table I).

About 60.7% of male participants belonged to the highest tertile, whereas 62.5% of female participants belonged to the lowest tertile among the studied population, which is statistically significant. (figure 1)

Figure 1: Bar diagram showing mean serum concentration in both genders. The graph shows that 60% of male participants belonged to higher tertile ranges, whereas 62% of females belonged to lower contents of ferritin tertile.

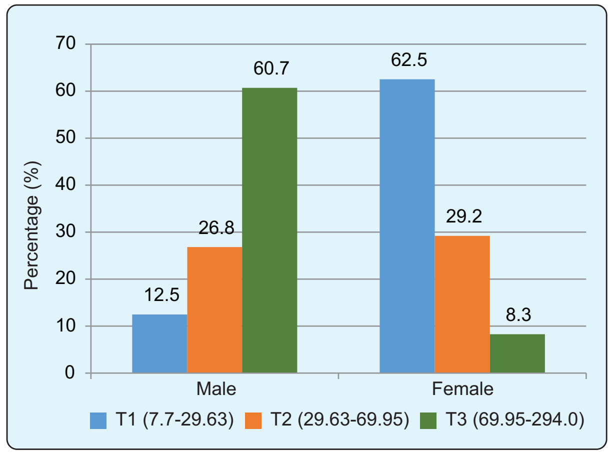

Figure I: Mean ferritin concentration (ng/ml) of study subjects, both male and female.

The standard reference interval of serum ferritin has a wide range because of age and gender variations.

The reference range for adult males is between 20-270 µg/L and that of adult females is 10-120 µg/L.[28] In the current study, we also observed that ferritin distribution was positively skewed. Further analysis for examining gender differences across ferritin tertiles revealed that in males, higher ferritin levels were linked

Table I: characteristics of the studied population.

Variables	Male	Female	p value
Age (years)	41.46 ± 9.40	38.08 ± 10.26	0.155
BMI (kg/m^2)	25.54 ± 2.65	25.40 ± 4.49	0.854
SBP (mmHg)	121.07 ± 10.48	117.50 ± 11.80	0.182
DBP (mmHg)	80.71 ± 7.94	79.38 ± 10.25	0.529
WC (inch)	91.32 ± 8.40	89.29 ± 12.31	0.394
WHR	0.90 ± 0.12	0.86 ± 0.11	0.187
FPG(mmol/L)	6.28 ± 2.20	6.37 ± 1.58	0.860
S.insulin (µU/mL)	8.84 ± 4.07	9.58 ± 4.03	0.475
HOMA -I.R.	1.23 ± 0.62	1.31 ± 0.55	0.603
Serum Ferritin (ng/ml)	98.72 ± 66.39	36.20 ± 45.15	Â0.001

Data were expressed as mean±SD
Unpaired t test was performed to compare between male and female.

to older age, increased BMI, elevated fasting plasma glucose (FPG), and higher serum insulin and Homeostatic Model Assessment for IR (HOMA-IR). In females, older age and elevated FPG were associated with higher ferritin tertiles. Still, there were no significant differences in serum insulin and HOMA-IR across these tertiles (Table II).

Multiple linear regression analyses showed a significant positive association between serum ferritin and fasting plasma glucose in (model II) in both males and females ($p < 0.001$) (Table III) after adjustment of other variables.

Additionally, in males, serum ferritin was positively associated with serum insulin ($p < 0.001$) and HOMA-IR ($p < 0.001$) after adjusting for other variables (Fig II, III). However, no significant relationship was found between serum ferritin and serum insulin or HOMA-IR in females. These findings highlight gender-specific differences in the associations between serum ferritin levels and metabolic parameters, providing valuable insights into the role of ferritin in developing diabetes mellitus, especially in males.

Figure II. showing the correlation between serum insulin and serum ferritin in males and females. In the graph, it is visible that the two variables are positively and significantly correlated ($p < 0.001$) in male but not in female subjects.

Figure III: shows the correlation between HOMA-IR and serum ferritin in male and female subjects. In the graph it is clearly visible that the two variables are positively and significantly correlated ($p < 0.001$) in male but not in female subjects.

Table II: characteristics of study subjects based on serum ferritin tertile categories.

Variables	Serum ferritin tertile (ng/mL)‘			*p*-value
	T1 (7.7– 29.63)	T2 (29.63–69.95)	T3 (69.95–294.0)	
(Male=92)				
Age (years)	32.71±3.09	41.47±9.20	43.26±9.49	<0.05
BMI (kg/m^2)	24.33±2.43	24.66±3.07	26.26±2.30	<0.05
SBP (mmHg)	120.00±8.16	118.33±10.97	122.50±10.68	0.429
DBP (mmHg)	80.00±8.16	77.67±7.99	82.21±7.71	0.179
WC (inch)	88.43±7.68	89.13±10.08	92.88±7.56	0.223
WHR	0.81±0.20	0.89±0.12	0.92±0.08	0.079
FPG(mmol/L)	5.12±0.45	5.30±0.58	6.99±2.56	<0.01
S.insulin (µU/mL)	5.51±2.08	6.98±2.52	10.35±4.22	<0.01
HOMA -IR.	0.71±0.28	0.92±0.34	1.48±0.65	<0.001
(Female=48)				
Age (years)	34.73±8.59	40.86±10.68	53.50±2.12	<0.05
BMI (kg/m^2)	24.19±3.59	26.53±5.77	30.50±0.71	0.126
SBP (mmHg)	113.67±11.41	122.14±9.06	130.00±14.14	0.080
DBP (mmHg)	76.67±11.13	82.86±7.56	87.50±3.54	0.217
WC (inch)	88.73±10.92	88.00±15.53	98.00±14.14	0.595
WHR	0.85±0.10	0.86±0.11	0.95±0.21	0.500
FPG(mmol/L)	5.85±0.54	6.50±1.43	9.75±3.75	<0.01
S.insulin (µU/ml)	9.06±3.93	9.71±3.99	13.05±5.73	0.437
HOMA -IR.	1.22±0.53	1.34±0.56	1.85±0.64	0.322

Data were expressed as mean±SD
ANOVA test was performed to compare the three tertile groups.

Table-III: Multiple regression analysis of the relation between FPG and variables of interest in male and female subjects

Variables	Male (n=92)				Female (n=48)			
	Model 1(R^2=.452)		Model-2(R^2=.523)		Model 1(R^2=.672)		Model-2(R^2=.741)	
	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
Age (yrs)	.352	<0.001	.231	<0.05	.398	<0.05	.237	.147
BMI (kg/m^2)	.132	.199	.076	.432	.459	Â0.01	.448	Â0.01
SBP (mmHg)	-.090	.467	-.030	.800	-.568	Â0.01	-.595	Â0.01
DBP (mmHg)	.157	.204	.109	.347	.599	Â0.01	.628	Â0.01
WHR	-.059	.606	-.041	.704	-.587	Â0.001	-.535	Â0.01
S.ferritin (ng/ml)			.341	Â0.001			.337	Â0.01

a. Dependent Variable: Plasma Glucose (mmol/L)

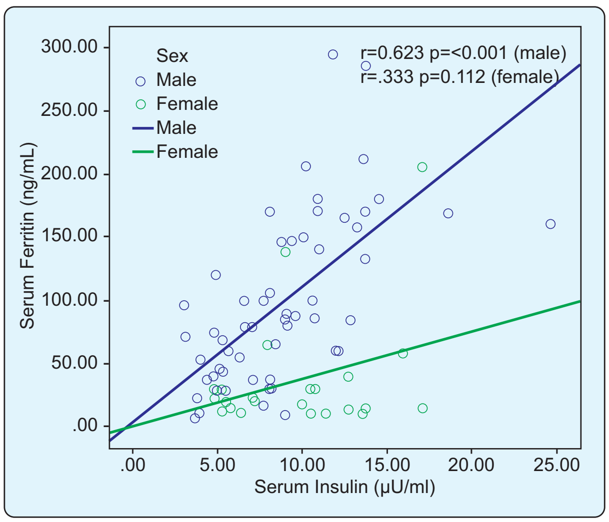

Figure 2: Correlation of serum ferritin (ng/mL) with serum insulin (µU/ml) in male and female subjects.

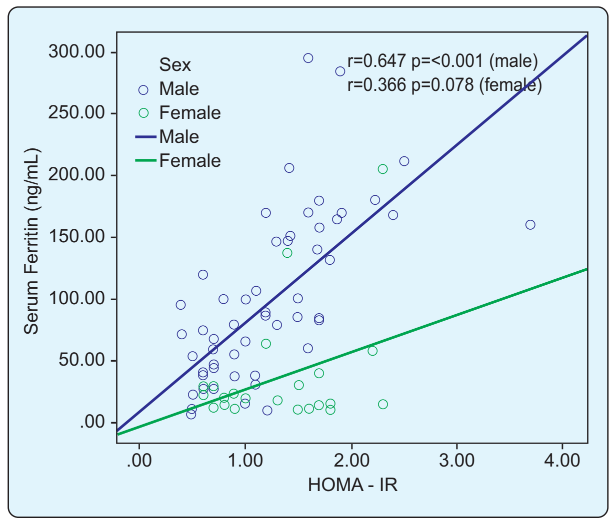

Figure 3: Correlation between serum ferritin (ng/mL) and HOMA-IR in male and female subjects

Discussion

This research investigated the link between serum ferritin levels and insulin resistance (IR) markers, including fasting insulin, glucose, and HOMA-IR, in Bangladeshi adults, uncovering significant insights into the mechanisms underpinning this association. The study revealed that individuals in the higher ferritin tertile were generally older and had a significantly higher BMI (Table I), consistent with previous studies[2], which have illuminated compelling links between elevated serum ferritin, aging, higher BMI, and an augmented risk of insulin resistance. Ferritin concentrations were higher among men than women (98.72 ± 66.39 versus 36.20 ± 45.15,Â0.001) (Table I), attributed to iron loss during menstruation[29]. These levels were comparable to those reported by Kim.[9] in Korean women. Mean ferritin concentration is lower in female subjects as they are within the reproductive age range. This observation emphasizes the necessity of considering physiological differences between sexes when examining iron metabolism and its implications for insulin resistance.

Our study underscored that individuals in the higher ferritin tertile exhibited elevated serum insulin and HOMA-IR values (Table II), indicating compromised glucose metabolism. This aligns with earlier research[3,9], particularly a prospective study conducted in France over a 6-year period, which established a direct correlation between higher serum ferritin levels and the risk of hyperinsulinemia and high HOMA-IR in both genders[3]. A significant and positive correlation between serum ferritin and IR markers (Serum insulin, glucose, and HOMA-IR) was observed in males. A similar observation was reported in some studies.[9,16] Unlike in men, the present study failed to find a significant association between serum ferritin and IR markers in women. Yue, et al.[30] observed that elevated ferritin levels correlated with insulin resistance in females but not males. The consistency of these findings across diverse populations underscores the robustness of the association between ferritin and insulin resistance.

Upon adjusting for confounding variables, multiple regression analysis highlighted a significant association of serum insulin and HOMA-IR with serum ferritin in males (Table III), confirming previous study.[31-32]

A critical facet of our study involved exploring potential mechanisms underlying the unfavorable association between increased serum ferritin and insulin resistance. Our considerations encompassed oxidative stress, inflammation, interference with hepatic insulin extraction, and impaired glucose utilization in adipocytes as potential contributors.[10,33-35] These proposed mechanisms resonate with existing literature, highlighting the multifaceted nature of this relationship and suggesting that iron, functioning as a pro-oxidant, could disrupt insulin signaling at the cellular level.

Our study identified hyperferritinemia as an early indicator of insulin resistance before the overt manifestation of diabetes.[32,36] prospective studies corroborated that elevated iron storage, even within clinically high-normal ranges, can induce insulin resistance, leading to diabetes, irrespective of race and obesity. This association was marked by elevated fasting insulin, glucose, and HOMA-IR levels. Monitoring serum ferritin levels could offer a valuable tool for timely identification and preventive interventions in at-risk individuals.

Interestingly, interventions such as blood donation and bloodletting aimed at reducing excess iron levels were discovered to impact insulin sensitivity positively[10]. This underscores the pivotal role of iron metabolism in diabetes risk and suggests potential avenues for intervention and prevention strategies. The research underscores the potential of serum ferritin as a biomarker for screening IR, especially in males at risk of developing diabetes. These findings highlight the importance of considering gender-specific variations and iron metabolism in understanding the complexities of insulin resistance and diabetes, paving the way for targeted interventions and risk reduction measures.

Conclusion.

In conclusion, our study illuminated a noteworthy link between serum ferritin levels and markers of insulin resistance, primarily evident in male participants. Those in the higher and middle tertiles of serum ferritin exhibited significantly elevated fasting glucose, serum insulin, and HOMA-IR values compared to their counterparts in the lowest tertile. This positive correlation between serum ferritin and insulin resistance markers was specific to male participants, as no such association was identified among women. Further evaluations of the variation in sex differences in these associations are warranted to understand the mechanisms behind these gender differences.

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