Ferritin as a marker of Insulin Resistance in Diabetic Patients

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Abstract:

Backgroud : Insulin resistance is a pathogenic hallmark of type 2 diabetes mellitus (T2DM).Serum ferritin, a predominant iron-storage protein and a biomarker of iron stores, are elevated in persons with prevalent diabetes as compared with non-diabetic controls and correlate with impaired fasting glucose levels.High ferritin levels have been associated with the metabolic syndrome and measures of insulin resistance .**The aim of the current study :** is to measure Serum Ferritin in patients with type 2 diabetes in Beni- Suef governorate and to study the relationship between serum Ferritin and Insulin Resistance. **Patients and Methods :** This study involved 40 patients with type 2 diabetes (24 females and 16 males) and 20 healthy adults (12 females and 8 males) served as a control group. All groups included in this study were subjected to Full History Taking, Clinical Examination including (BMI & Waist Circ.) and Laboratory Investigation including (FPG, HbA1c, Serum Ferritin and Fasting Serum Insulin & measuring HOMA-IR).**Results :** Ferritin showed a statistically significant correlation with Waist Circ., FPG, HbA1c, Fasting Serum Insulin and Insulin Resistance (HOMA-IR) in the diabetic group (P < 0.05) .**Conclusion:** Serum ferritin can be used as a marker of insulin resistance syndrome in diabetics

Keywords: Ferritin, Insulin Resistance, Type 2 Diabetes.

1. Introduction:

Insulin resistance is a pathogenic hallmark of type 2 diabetes mellitus (T2DM) [1]. Ferritin is the main iron storage protein of the body with a critical role in iron homeostasis. In the clinical setting, measurement of circulating ferritin is used extensively in the diagnosis of iron-related disorders [2]. The interpretation of an elevated serum ferritin requires consideration of several separate disease categories including; Iron overload, Acute inflammatory conditions, Liver disease, [3] levels of serum ferritin, a predominant iron-storage protein and a biomarker of iron stores, are elevated in persons with prevalent diabetes as compared with non-diabetic controls and correlate with impaired

fasting glucose levels [4]. High ferritin levels have been associated with the metabolic syndrome and measures of insulin resistance [5].

Several markers of iron metabolism are associated not only with Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) but also with adipocyte IR in humans. These findings suggest that body iron stores and/or iron metabolism–related factors may contribute to the induction of IR early in the pathogenesis of T2DM [6]. Iron is an important catalyst in the formation of highly reactive hydroxyl radicals, and intracellular reactive oxygen species have been shown to play an important causal role in the induction of insulin resistance (IR) [7], consequently, massive iron overload, as present in hereditary hemochromatosis, frequently leads to diabetes [8]. In addition, recent data have shown that modest iron overload (i.e., iron markers within the normal range) may also be involved in the pathogenesis of type 2 diabetes mellitus (T2DM) in general. Prospective studies have linked serum ferritin, the most reliable marker of body iron stores, and dietary heme iron intake to incident T2DM [9]. Several cross-sectional and longitudinal studies have shown that serum ferritin is associated with muscle IR measured by homeostasis model assessment (HOMA-IR) or by hyperinsulinemic euglycemic clamp [10].

The aim of the present study is to measure serum Ferritin in patients with type 2 diabetes in Beni-Suef governorate and to study the relationship between serum Ferritin and Insulin Resistance.

2. Patients and Methods:

This study involved 40 diabetic patients (24 females and 16 males) diagnosed according American Diabetic Association (ADA, 2014) criteria [11] were selected from the outpatient clinic of the internal medicine department Beni-Suef University Hospital and 20 healthy adults (12 females and 8 males) served as a control group.

2.1 Exclusion criteria:

Patients with history of recent iron intake, blood transfusion, acute or chronic infection and chronic liver disease.

2.2 All groups included in this study were subjected to:

A. History and Clinical Examination:

- Including measurement of Arterial Blood Pressure (ABP).

- Height was measured without shoes, Weight also was measured with light clothes.

- Body Mass Index (BMI) was calculated with weight in Kg divided by the squared height in meters (Kg/m2).

- Waist circumference was measured at mid way between the inferior margin of the last rib and the iliac crest in horizontal plane on standing position with wide base gait and arms beside the body.

B -Laboratory Investigations :

Fasting Plasma Glucose (FPG), Glycated Hemoglobin (HbA1c), Fasting Serum Insulin (FI) and Serum Ferritin were done then measuring Insulin Resistance by Homeostasis Model Assessment (HOMA-IR) [12].

HOMA-IR =

$$\frac{\text{Fasting Insulin ((mU/L)) x Fasting plasma glucose (mmol/L)}}{22.5}$$

- **Ferritin:**

Phoenix Pharmaceutical's Human Ferritin ELISA Kit is designed to measure the concentration of Ferritin from human serum (Normal Range 28-365 ng/ml).

- **Insulin:**

Phoenix Pharmaceutical's Human Insulin ELISA Kit is designed to measure the concentration of Human Insulin from human serum/plasma (Normal Range 2.5-7.1 µlU/mL).

2.3 Statistical methodology:

• Analysis of data was done by IBM computer using SPSS (statistical program for social science) as follows;

- Description of quantitative variables as mean, SD and range.

- Description of qualitative variables as number and percentage.

- Unpaired t-test was used to compare quantitative variables, in parametric data (SD < 50 % mean)

• P value > 0.05 insignificant

• P < 0.05 significant

• P < 0.01 highly significant.

3. Results:

This study was carried out on 40 patients with T2DM were selected from the outpatient clinic of the internal medicine department Beni-Suef University Hospital and 20 healthy subjects as a control group within six months from June to December 2014.

3.1-Demographic features of subjects under study:

Patients group including 16 males (40%) and 24 females (60%), their age ranged from 32 to 63 years with a mean of (48.30±10.42), 16 patients were hypertensive (40%) and 24 patients were not hypertensive (60%).

Control group including 8 males (40%) and 12 females (60%), their age ranged from 37 to 60 years with a mean of (45.80±7.88).

3.2-Clinical features of subjects under study:

Patients group; Their Weight ranged from 66 to 110 Kg with a mean of (86.10±12.34), Height ranged from 155 to 170 cm with a means of

(165±4.94), BMI ranged from 26 to 42 Kg/m2 with a mean of (32±4.71) and Waist Circ. ranged from 95 to 130 cm with a mean of (110±11.99).

Control group; Their Weight ranged from 72 to 95 Kg with a mean of (82.60±8.84), Height ranged from 155 to 170 cm with a mean of (164.40±5.17), BMI ranged from 26 to 33

Kg/m2 with a mean of (30.20±2.86) and Waist Circ. ranged from 75 to 100 cm with a mean of (87±9.51).

3.3- Laboratory features of subjects under study:

Patient group; Their Fasting Plasma Glucose (FPG) ranged from 200 to 389 mg/dl with a mean of (247.60±56.18) (normal 70-100 mg/dl),

Fasting Insulin (FI) ranged from 3.80 to 21.80 μlU/mL with a mean of (10.78±5.50) (normal 2.5-7.1 μlU/mL), HbA1c ranged from 7.50 to 11.00% with a mean of (9.30±1.20) (normal 4% - 5.6%), HOMA-IR range varied from 2.00 to 11.84 % with a mean of (6.32± 2.85) (normal <2 %) and Ferritin ranged from 135 to 697 ng/ml with a mean of (332.10 ±195.35) (normal 28-365 ng/ml) .

Control group; Their FPG ranged from 80 to 105 mg/dl with a mean of (94± 8.83), Fasting insulin ranged from 4.5 to 7 μlU/mL with a mean of (5.7± 0.90), HbA1c ranged 4 to 5.20 % with a mean of (4.82 ± 0.44), HOMA-IR ranged from 1.11 to 1.60 % with a mean of (1.31± 0.20), Ferritin ranged from 44 to 281ng/ml with a mean of (169.40± 81.22).

3.4 Comparison between Patients and Controls regarding Demographic features:

In our study, we found that no significant correlation between patients and controls regarding Age (P=0.35) & Gender (P=0.61). However, there was a statistically significant correlation regarding hypertension between patients and controls (P<0.001*) Table (1).

3.5- Comparison between Patients and Controls regarding Clinical features:

In our study, we found that no significant correlation between patients and controls regarding Weight (P<0.26), Height (P<0.66) and BMI (P<0.12). However, there was a statistically significant correlation regarding Waist Circ. between patients and controls (P<0.001*) Table (2) & Fig (1).

3.6- Comparison between Patients and Controls regarding Laboratory features:

In our study, we found a statistically significant correlation between patients and controls regarding FPG (P<0.001*), HbA1c (P<0.001*), Fasting Insulin (FI) (P<0.001*), Insulin Resistance (HOMA-IR) (P<0.001*) and Serum Ferritin (P<0.001*) Table (3) Fig (2).

3.7-Correlation Between Ferritin Levels And Other Disease Parameters Among Diabetic Patients Under Study:

In our study, we found a statistically significant positive correlation in patients group between Ferritin and age (P=0.018), Waist Circ.

(P<0.001), FPG (P=0.001), HbA1c (P<0.001), Fasting Insulin (P=0.023) and Insulin Resistance (HOMA-IR) (P=0.002). However, there was no significant correlation in patients group between Ferritin and BMI (P=0.483) Table (4).
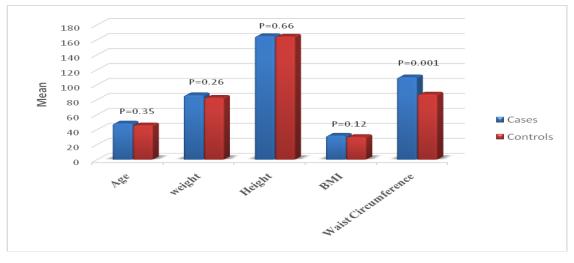
Table (1): Comparison between Patients and Controls regarding Demographic Features

	Patients (n=40)		Controls (n=20)		P-Value
Age(years) **Mean±SD**	48.30±10.42		45.80±7.88		0.35 (NS)
Gender	16 ♂ (40.0%) 24♀ (60.0%)		8♂ (40.0%) 12♀ (60.0%)		0.61 (NS)
HTN	HTN	16 (40.0%)	HTN	0	0.001* (S)
	Non-HTN	24 (60.0%)	Non-HTN	20	

Table(2): Comparison between Patients and Controls regarding Clinical features

	Subjects	N	Mean	Std. Deviation	P value
Weight (Kg)	Cases	40	86.10	12.36	0.26
	Controls	20	82.60	8.84	
Height (Cm)	Cases	40	165.00	4.94	0.66
	Controls	20	164.40	5.17	
BMI (Kg/m2)	Cases	40	32.00	4.71	0.12
	Controls	20	30.20	2.86	
Waist Circ. (Cm)	Cases	40	110.00	11.98	0.001*
	Controls	20	87.00	9.51	

Fig (1) Comparison between Patients and Controls regarding Clinical features

Table (3): Comparison between Patients and Controls regarding Laboratory features

	Subjects	N	Mean	Std. Deviation	P value
FPG (mg/dl)	Cases	40	247.60	56.18	*0.001**
	Controls	20	94.00	8.83	
Fasting Insulin (μlU/mL)	Cases	40	10.78	5.50	*0.001**
	Controls	20	5.70	0.90	
HbA1c (%)	Cases	40	9.30	1.20	*0.001**
	Controls	20	4.82	0.44	
Ferritin (ng/ml)	Cases	40	332.10	195.35	*0.001**
	Controls	20	169.40	81.23	
HOMA-IR (%)	Cases	40	6.32	2.85	*0.001**
	Controls	20	1.31	0.21	

Fig (2) comparison between Patients and Controls regarding Laboratory features

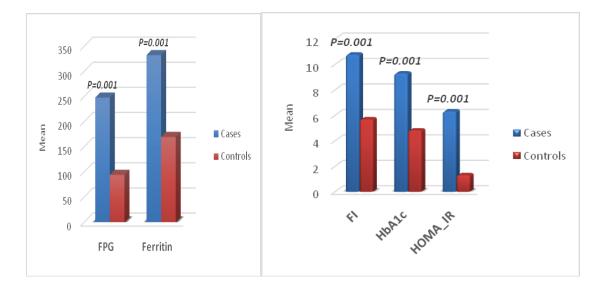**Table (4): Correlation between Ferritin and other disease parameters in diabetic patients group**

Correlating Variables		Ferritin
Age	R	.304*
	P value	.018
BMI	R	-.092
	P value	.483
Waist Circ.	R	.488**
	P value	.000
FPG	R	.401**
	P value	.001
FI	R	.294*
	P value	.023
HbA1c	R	.549**
	P value	.000
HOMA_IR	R	.390**
	P value	.002

4. Discussion:

Our study carried on 40 diabetic patients 16 males and 24 females, their age ranged from 32 to 63 years, 16 patients were hypertensive and 24 patients were non-hypertensive and 20 healthy controls 8 males and 12 females, there age ranged from 37 to 60 years, which history taken ,clinical examination including (ABP ,Weight , Height , BMI, and Waist Circ.) and laboratory investigations including (FPG, HbA1c , Fasting Serum Insulin, Serum Ferritin and measuring HOMA-IROur study showed a statistically significant higher serum ferritin in type 2 diabetes mellitus patients compared with controls (P=0.001). Also ferritin showed a statistically significant positive correlation with Age (P=.018), Hypertension (P=0.001), Waist Circ. (P<0.001), FPG (P=0.001), HbA1c (P<0.001), Fasting Insulin (P=0.023) and Insulin Resistance (HOMA-IR) (P<0.002) but with BMI was insignificant (P=0.483).

In agreement with our results [13] study which done over 423 subjects from the PREDIMED study (The PREDIMED study is a multicenter, randomized clinical trial conducted in Spain to assess the effects of the Mediterranean diet on the primary prevention of cardiovascular disease) observed that serum ferritin was positively correlated with increased glucose and insulin circulating levels but also with HOMA IR . Also [14] a 4 year longitudinal observational study was conducted at the Asan Medical Center, Seoul, Republic of Korea. The study population consisted of 2,029 men without type 2 diabetes who underwent routine health examination in 2007 (baseline) and 2011 (follow-up) observed a significant positive correlation between the level of ferritin and HOMA-IR. Another study [5] subjects participated in a nationwide epidemiological survey on metabolic disorders in the adult German population. 1200 participants included in this had shown that serum ferritin is positively correlated with elements of the insulin resistance syndrome in representative German population and also found increased blood pressure was also significantly associated with increased serum ferritin.

In our study we found increasing in FPG, ABP and Waist Circ. In hypertensive diabetic group which may be components of metabolic syndrome with significant higher in ferritin, In agreement with this[16] study aimed to explore the relationship between serum ferritin and metabolic syndrome in Chinese population carried on 8,441 adults confirmed that there was a positive association between higher ferritin levels and the prevalence of metabolic syndrome or metabolic syndrome components in different sex groups.

A cross-sectional study [17] using representative data from the general U.S. population (6,044 adults).

Elevated iron stores reflected as serum ferritin were positively associated with the prevalence of the metabolic syndrome and with insulin resistance, these associations were evident at moderately elevated iron levels, below levels associated with hemochromatosis. Also [18]the aims of the study were 1) to compare the ferritin levels, and to investigate the relationships between ferritin, high-sensitivity CRP (hs-CRP), fasting glucose, fasting insulin and homeostasis model assessment (HOMA-IR) levels in elderly patients, study population included 121 elderly patients from Turkey found mean levels of ferritin were increased in elderly patients with metabolic syndrome. And also, ferritin levels were positively correlated with systolic and diastolic blood pressures as well as fasting insulin but not with high-sensitivity CRP (hs-CRP) levels in elderly patients with metabolic syndrome.

In contrast to our results[19], his study was on 84 type 2 diabetes mellitus patients and 60 healthy control group and he had found

increased serum ferritin concentration in diabetic group compared with control group. Serum ferritin levels are increased in Type 2 diabetic patients in the absence of a reciprocal decrease of soluble transferrin receptor (sTfR). This finding suggests that elevated ferritin levels in Type 2 diabetes are mainly as a result of inflammatory mechanisms rather than iron overload.

Another study [20] had evaluated fifty type 2 diabetic patients attend to Korea University Hospital and twenty-five healthy non-diabetic subjects had acted as a control group. The results showed that the value of log ferritin was higher in the type 2 diabetes patients than the control subjects, but not at a statistically significant level.

Another one [21] had showed that there was no correlation between serum ferritin and HbA1c in diabetic patients of either sex, ferritin levels in patients with DM is high, but not related to levels of HbA1c and blood glucose control.

5. Conclusion and Recommendations:

Serum ferritin may be a marker of not only glucose homeostasis but also some components of insulin resistance syndrome in diabetics. This study can be done on a larger number of patients including other governorates in Egypt with correlation between ferritin level and diabetic complications.

6. References:

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