The Egyptian Journal of Hospital Medicine (Jul. 2016) Vol. 64, Page 405- 410

The Relationship between Serum Ferritin and Glycosylated Hemoglobin in Adults with Type 2 Diabetes Mellitus

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ABSTRACT
Background: serum ferritin, an acute phase reactant is a marker of iron stores in the body. Several studies concluded that, serum ferritin was found to be high in uncontrolled type 2 diabetic patients. This study was carried out to investigate serum ferritin levels in poor controlled type 2 diabetes (PCD) and well controlled type 2 diabetes (WCD). **Subjects and Methods:** the study comprised of 42 apparently healthy controls and 84 type 2 diabetic patients. They were recruited from the Governmental and NGO's Hospital at Cairo, Egypt. Anthropometric measurements including: weight and height were measured and body mass index (BMI) was calculated. Fasting blood glucose (FBG); Glycosylated hemoglobin (HbAIc) and serum ferritin were determined. Patients were subdivided into PCD and WDC according to HbAIc levels. **Results**: BMI; FBG; HbAIc and serum ferritin were significantly higher in in type 2 diabetics compared with apparently healthy controls. Based on glycemic control; the levels of FBG and serum ferritin were elevated in patients with HbA1c >7. Moreover, there was a positive significant correlation between serum ferritin, HbA1c and FBG that was more pronounced in PCD patients. **Conclusion**: the present study showed positive association of serum ferritin levels with glycemic control in Type 2 diabetic patients.
Keywords: Type 2 diabetes- Fasting blood glucose- Glycosylated haemoglobin- Serum ferritin- glycemic control

INTRODUCTION
Diabetes mellitus is one of the most common problems caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cells [(1)]. Type 2 diabetes has a rising attitude globally. The worldwide spread of diabetes among general population is estimated to increase to 300 million in 2025 [(2,3)].

Elevated iron stores may increase the risk of developing diabetes. Emerging scientific evidence has revealed unsuspecting influences between iron metabolism and type 2diabetes. The relationship is bi‑directional, iron affects glucose metabolism, and glucose metabolism impinges on several iron metabolic pathways. It is increasingly recognized that iron influences glucose metabolism، even in the absence of significant iron overload [(4)].

Although a mechanism linking iron concentrations and diabetes is not established, it is known that iron is a catalyst in the formation of hydroxyl radicals, which may contribute initially to insulin resistance, subsequently to decreased insulin secretion, and ultimately to the development of type 2 diabetes [(5)]. Animal models suggest that iron excess may result in beta-cells oxidative stress and decreased insulin secretion [(6)].Ferritin is a specialized iron storage protein, which reflects iron stores in the body [(7)].

It has been used as a surrogate variable to reflect body iron stores in healthy individuals. Previous studies have demonstrated an association between increased SF levels and higher risks of diabetes [(8, 9)].

Glycosylated hemoglobin (HbA1c) is a stable, irreversible product of non-enzymatic glycosylation of the hemoglobin β-chain by serum glucose. HbA1c is used as an indicator for the state of glycemic control, progression of the disease and development of complications in diabetic patients [(10, 11)].

The present study is undertaken to estimate the association between serum ferritin, FBG and glycemic control in type 2 adult diabetes mellitus.

SUBJECTS AND METHODS
Subjects:
This study comprises eighty four adult patients with type 2 diabetes mellitus (treated with hypoglycemic drugs) as well as forty two ages and sex matched apparently healthy adults serve as a control group. They were recruited from the Governmental and NGO's Hospital at Cairo, Egypt. Diabetic patients met the criteria

Received: 17/08/2016
Accepted: 25/08/2016
DOI: 10.12816/0029032

of **American Diabetes Association** [12]. Subjects of the control group were confirmed by fasting blood glucose to be non-diabetic. The study was conducted after obtaining a permission from Ethical Committee of the GOTHI (**G**eneral **O**rganization for **T**eaching **H**ospitals and **I**nstitutions), and informed consent were taken from all subjects before commencing the study.

The inclusion criteria include type 2 diabetic adults (both sexes) in the age group of 35–45 years, without complications.

Exclusion criteria

- Subjects received any medication other than insulin or complained from any acute or chronic illness other than diabetes mellitus.
- Subjects have anemia therapy, acute and chronic inflammation and blood transfusion that could affect ferritin levels.

All individuals included in this study were subjected to the following:

1- Anthropometric measurements, including height and weight were obtained while the subjects were in light clothing and not wearing shoes. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Anthropometric indices were measured according to standardized methods of **WHO** [13].

2- Laboratory measurements

After an overnight fast, blood samples were antecubital vein into vacationer tubes, FBG was determined according to [14]. The method of **Abraham *et al*.** [15] was used for blood HbA1c determination. Serum was separated by centrifugation and used for determination of ferritin using kit protocol (Cat.No.:EK-310-25) provided by PHOENIX PHARMACEUTICALS, INC (Burlingame CA). Diabetic patients were categorized according to their HbA1c values into two sub-groups: Well controlled diabetic (WCD) with HbA1c value ≤7.0 % (and uncontrolled diabetic (UCD) with HbA1c value >7.0% according to **Rohlfing *et al*.** [16].

Statistical Analysis:

All analyses were performed using the SPSS 19.0 statistical software (SPSS 19.0 for Windows; SPSS, Inc., Chicago, IL). Values were expressed as mean with standard deviation mean. Comparisons were done between the three groups using analysis of variance (ANOVA) followed by post hock Duncan analysis. Pearson Correlation analysis was used to examine the association between serum ferritin and other variables, Pearson Correlation analysis was tested. $P < 0.05$ was considered statistically significant.

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RESULTS

The present study was done on 84 type 2 diabetic patients (40 male and 44 female, age range: 35-45 years with mean age of 40±5.4. Age and sex matched healthy subjects (20 male and 22 female) were used as normal control. When cases were grouped according to glycemic control (HbA1c values), WCD (HbA1c ≤ 7%), included 38 patients (18 male and 20 female) and PCD (HbA1c <7%) included 46 patients (22 male and 24 female),

There was a significant elevation in BMI as well as in the levels of FBG, HbA1c and serum ferritin of diabetic patients compared with normal control group (table 1). There was also a significant increase in BMI with mean value of 26.03±2.28 and 27.93±2.48 for WCD and PCD, respectively as compared to normal control (23.80±3.34). However, no significant differences were observed in BMI value between male and female of each glycemic status (figure 1).

Significant pronounced increase was detected in FBG of PCD (311.45±21.19 mg/dl) compared to (173.38±13.61 mg/dl) in WCD (figure 2). Moreover, the differences between the two glycemic groups and normal control (87.35±8.55 mg/dl) were significant ($p < 0.05$). Furthermore, FBG levels of male and female of both glycemic statuses were significantly higher than their corresponding controls. No significant differences were found between FBG of male and female with WCD, while the levels in females FBG with PCD were significantly lower ($p < 0.05$) than their corresponding males (figure 2).

Comparing to corresponding controls, % blood HbA1c of PCD & WCD (total diabetic patients, male and female) were significantly higher (figure 3). Moreover, the difference between PCD & WCD of diabetic patients was significant, while no significant differences were detected between male and females of each glycemic status.

Serum ferritin was found to be significantly higher in diabetic cases with PCD (382.01±31.41 µg/ml**)** & WCD (163.09±22.62 µg/ml) than non-diabetic control (94.18±13.13 µg/ml**)** (figure 4). The effect of gender on serum ferritin levels showed significant differences between the two glycemic statuses of both sexes as compared to their corresponding controls.

However, serum ferritin levels of females were significantly lower than males ($p < 0.05$).

The correlations between serum ferritin versus BMI, FBG and HbA1c of the two glycemic status have been calculated with Pearson's correlation co‑efficient (r) has been calculated, and the r value with P was depicted in Table 2.

There was no statistical association was found between serum ferritin and BMI of all cases of diabetes. However, there was positive correlation between serum ferritin, FBS and HbA1c of diabetic patients; it was more pronounced in PCD than WCD (table 2).

DISCUSSION

The levels BMI, FBG, %HbA1c and serum ferritin were significantly higher in diabetic patients. Similar findings were observed by **Chandrashekhar *et al.*** [17] and **Kundu *et al***. [18].

Serum ferritin, a reflector of body iron stores was significantly higher in diabetic patients when compared to controls. This possibly reflects the subclinical hemochromatosis developing in a long standing diabetic patient [19]. **Fernandez *et al.*** [20] in their studies concluded that increased body iron stores are possibly associated with occurrence of glucose intolerance, type 2 diabetes and gestational diabetes.

Elevated ferritin levels were indicated to be due to elevated body iron stores or ferritin is an acute‑phase reactant and elevated ferritin may reflect inflammation or delayed clearance of glycosylated ferritin. It is also suggested that ferritin level is increased due to lack of glycemic control [21].

In our study, the more pronounced significant increase in serum ferritin levels was observed in poorly controlled type 2 diabetes compared to well controlled ones was consistent with the study of **Chandrashekhar *et al.*** [17], they confirmed that serum ferritin was increased in type 2 diabetic patients as long as glycemic control was not achieved. Moreover, **Cantur *et al.*** [22] confirmed in their studies that poorly controlled diabetes patients had hyperferritinemia. This showed that serum ferritin was increased in diabetes as long as glycemic control was not achieved. In diabetic subjects, a positive correlation between increased serum ferritin and poor glycemic control, reflected by higher HbAIc has been suggested by **Eschwege *et al.*** [23].

The observed decrease in mean serum ferritin concentrations in females compared with males of the present study was consistent with previous studies [24, 25]. It is suggested that this lower iron status in women is likely attributable to menstrual blood loss [26, 27].

Our study showed no correlation between serum ferritin and BMI in all cases. Similar results were reported by **Chandrashekhar *et al.*** [17] and **Raj *et al.*** [28] in type 2 diabetic men. On the contrary; significant correlation was reported by **Kundu *et al.*** [18].

In this study, we found that serum ferritin had a positive statistically significant correlation with FBS, HbA1C. These findings were consistent with study done by **Hee *et al.*** [29]**.** Similarly, other studies [30, 17] showed an independent positive association between serum ferritin concentration and FBS and HbA1C. The effect of lowering serum ferritin levels on metabolic control of type 2 diabetes mellitus was studied by **Cutler** [31], by giving Desferoxamine that it resulted in decrease in HbA1C in patients with poorly controlled type 2 Diabetes Mellitus. But, this was contradicted by **Redmon *et al.*** [32], who found no such benefit by decreasing serum ferritin levels.

CONCLUSION

According to the observations made in this study, it is evident that positive correlation exists between serum ferritin levels and glycemic control. This highlights the need for strict glycemic control in these subjects.

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Table (1): BMI; FBG; HbA1c and serum ferritin of diabetic patients &healthy control

Parameters	Normal control (n=42)	Diabetic patients (n=84)
BMI	23.88±3.34	26.98±4.27 [a]
FBG	87.35±15.32	272.55±13.63 [a]
HbA1c	5.42±0.81	8.76±0.63 [a]
Serum Ferritin	94.18±11.13	272.55±13.6 [a]

BMI: Body mass index- FBG: Fasting blood glucose- HbA1c: Glycated hemoglobin. $P < 0.05$ a: Significant difference between patients and control.

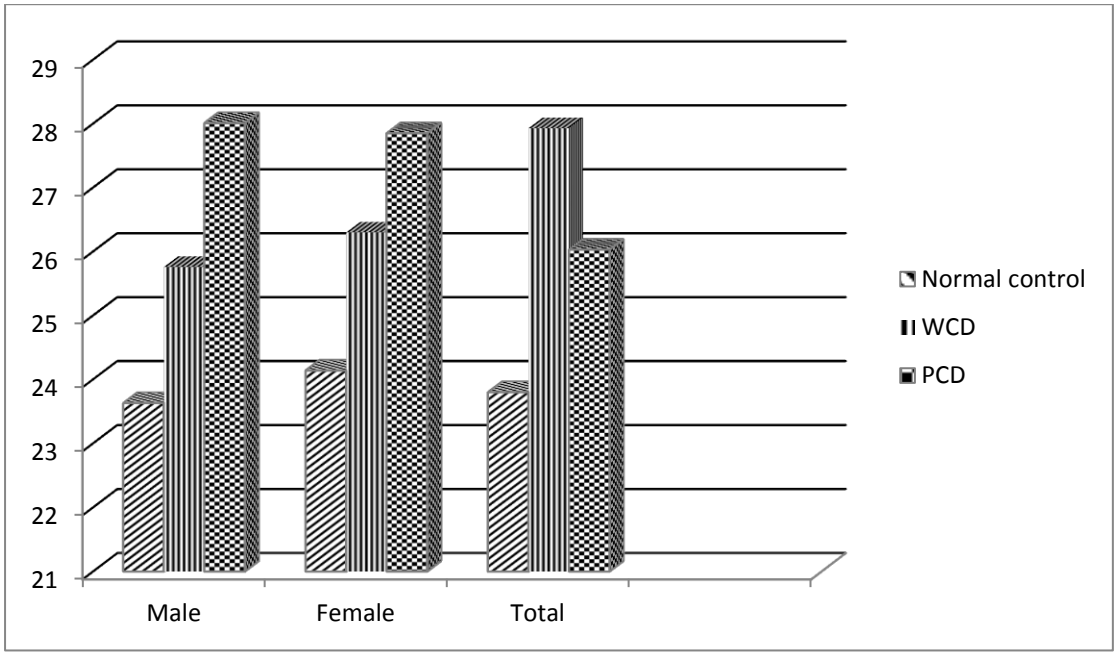

Figure (1): BMI of normal control and diabetic patients categorized by gender and glycemic control. BMI: Body mass index. PCD: Poor controlled diabetes. WCD: Will controlled diabetes. $p < 0.05$

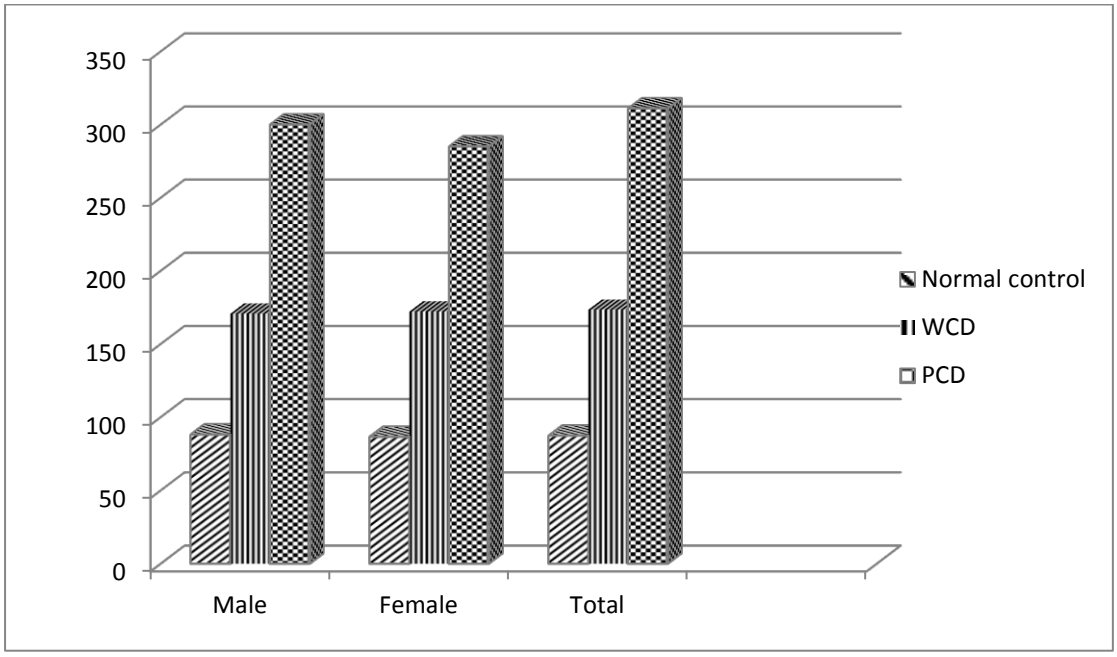

Figure (2): FBG of normal control and diabetic patients categorized by gender and glycemic control. FBG: Fasting blood glucose. PCD: Poor controlled diabetes, WCD: Will controlled diabetes. $P < 0.05$

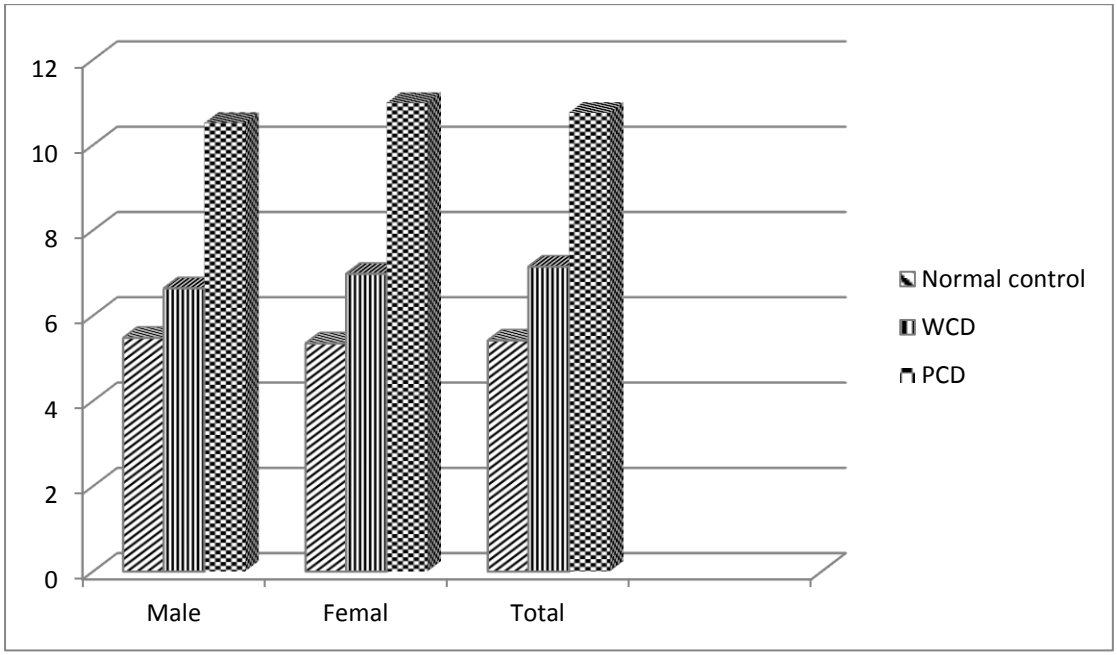

Figure (3): Blood HbA1c of normal control and diabetic patients categorized by gender and glycemic control. HbA1c: %Glycated hemoglobin. PCD: Poor controlled diabetes. WCD: Will controlled diabetes. $p < 0.05$

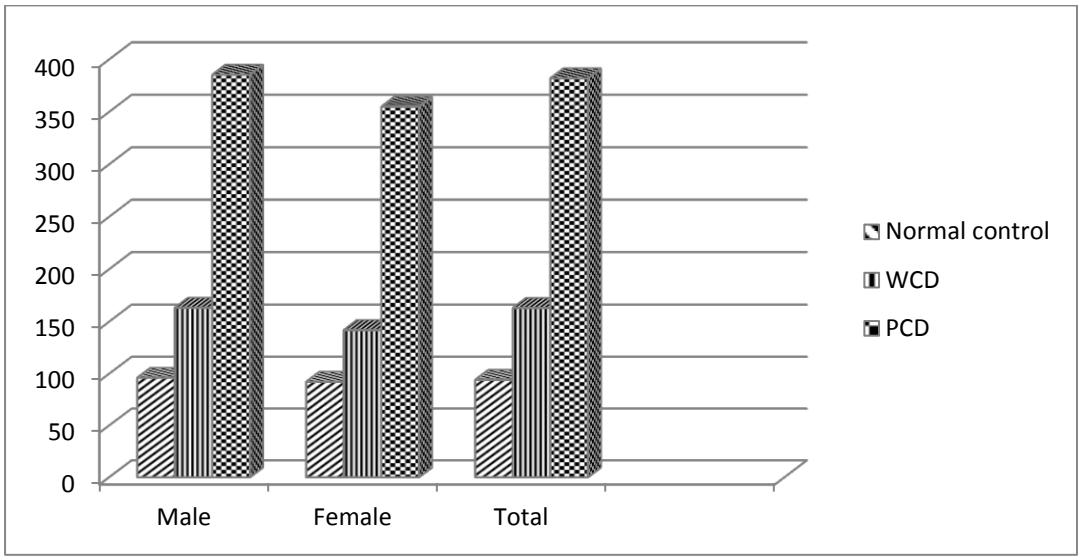

Figure (4): Serum ferritin of normal control and diabetic patients categorized by gender and glycemic control. PCD: Poor controlled diabetes. WCD: Will controlled diabetes $p < 0.05$

Table (4): Correlation between serum ferritin and the measured parameters in normal control & diabetic patients according to glycemic control and gender

Parameters	Male			Female			Total		
	Normal control	Patients		Normal control	Patients		Normal control	Patients	
		WCD	PCD		WCD	PCD		WCD	PCD
	r (p-value)			r (p-value)			r (p-value)		
BMI	0.836 (0.000)	0.055 (0.812)	-0.121 (0.601	0.283 (0.213)	-0.292 (0.200)	0.114 (0.623)	0.595 (0.000)	-0.078 (0.621)	0.110 (0.490)
FBS	-0.033 (0.886)	0.313 (0.027)	0.516 (0.01)	0.255 (0.265)	0.349 (0.003)	-0.587 (0.005)	0.133 (0.342)	0.309 (0.05)	0.460 (0.011)
HbAIc	0.190 (0.409)	0.771 (0.048)	0.608 (0.001)	0.153 (0.509)	0.460 (0.011)	0.508 (0.001)	0.194 (0.219)	0.732 (.046)	0.493 (0.006)

BMI: Body mass index FBG: Fasting blood glucose HbAIc: Glycated hemoglobin