

Serum ferritin in pre-diabetes & diabetes mellitus type 2 and its relationship with glycemic status

S. Kesav¹, D. Ponnudhali^{2,*}

¹UG Student, ²Associate Professor, Dept. of Biochemistry, Vinayaka Mission's Kirupananda Variyar Medical College, Salem

***Corresponding Author:**

Email: ponnudhalid@gmail.com

Abstract

Introduction: Emerging scientific evidence suggests an increased prevalence of elevated serum ferritin levels in diabetes mellitus type 2. Serum ferritin, being a reliable marker of body iron stores, have been related to glucose intolerance.

Aim and Objectives: To analyze the serum ferritin levels in individuals having pre-diabetes and diabetes and to study its association with fasting blood glucose levels.

Materials and Method: It is a cross-sectional study conducted in diabetic (n=40), pre-diabetic (n=40) and healthy individuals (n=40). Serum ferritin & fasting glucose levels were analyzed and compared among the groups. BMI was calculated and analyzed in all the groups.

Statistical analysis: Statistical analysis done using SPSS 23 software. Mean and standard deviations of the parameters were compared using one way Analysis of variance (ANOVA) and Pearson's correlations done for serum ferritin, glucose and BMI.

Results: Serum ferritin was found to be significantly increased ($p < 0.000$) in the diabetic ($74.68 \pm 22.74 \mu\text{g/l}$) compared to pre-diabetic ($47.53 \pm 14.46 \mu\text{g/l}$) and in pre-diabetic compared to healthy individuals ($25.0 \pm 1.71 \mu\text{g/l}$). Positive correlations were found among serum ferritin, fasting blood glucose and BMI.

Conclusion: Serum ferritin could have an influential role in glucose homeostasis and its elevation in pre-diabetes and diabetes could have important therapeutic and prognostic implications.

Keywords: Ferritin, Pre-diabetes, Oxidative stress, Fasting blood glucose, Diabetes mellitus type 2

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Introduction

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia, impaired Insulin secretion and insulin resistance. Recent studies have shown Insulin resistance syndrome (IRS) to be correlated with increased serum ferritin suggesting the pathophysiological link between the severity of IRS and the serum ferritin levels.^(1,2,3)

Pre-diabetes includes individuals with IFG (Impaired Fasting Glucose) and IGT (Impaired Glucose Tolerance). It is the 'grey area' between normal and diabetic blood sugar levels. Individuals with pre-diabetes are exposed to greater risk of developing diabetes and its related complications.

Serum iron and ferritin have currently been found to be strongly associated with pre-diabetes and type 2 Diabetes Mellitus. Serum Ferritin is a reliable marker of body Iron stores and hyperferritinemia have been linked to glycemic status of individuals and also known to correlate with the complications of Diabetes Mellitus like Retinopathy, Nephropathy, Neuropathy & Vascular dysfunction.⁽⁴⁾

Oxidative stress and Inflammation have vital role in the pathogenesis of Insulin resistance and type 2 Diabetes Mellitus.⁽⁵⁾ An important consequence of oxidative stress is insulin resistance and it is also implied in increasing ferritin synthesis. Oxidative stress, Hyperglycemia, Iron overload and Protein glycation could result in the development of Insulin resistance,

poor glycemic control and thereby early appearance of complications in Diabetes Mellitus.⁽⁶⁾

We have chosen to assess the association of serum ferritin to pre-diabetes and diabetes and tried to establish its role in glucose homeostasis.

Materials and Method

Study Design: We have conducted our study in Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Salem. This cross-sectional study had been conducted in 120 individuals: 40 healthy subjects formed the control group I and 40 patients diagnosed with type 2 Diabetes Mellitus formed the group 3. Another 40 individuals with fasting blood glucose levels between 100 to 125 mg/dl, and classified to be prediabetic (based on American Diabetic Association guidelines) belonged to group 2.⁽⁷⁾ Written consent was obtained from the participants and they were briefed about our protocol. This study was accepted and approved by the institutional ethics committee.

Subjects with the following disorders were eliminated from our study: cardiac/renal disease, hypertension, systemic illness, chronic infections, endocrine disorders, malignancy or neuropsychiatric illness. Chronic alcoholics and smokers were also excluded.

Subjects with Diabetes Mellitus Type 2 were included in group 3, healthy individuals without diabetes in group 1 and only pre-diabetic individuals (non-

diabetics) were included in group 2. All the relevant demographic data were collected and the subjects were age and sex matched. Anthropometric measurements including height and weight were measured to calculate BMI.

Sample collection and analysis: Fasting blood samples were collected from the subjects in all the 3 groups and the following analyses done.

1. Fasting plasma glucose, estimated by end-point method in semi autoanalyzer – MISPA EXCEL.
2. Serum ferritin analysed by latex turbidimetric method, using the same analyser.⁽⁸⁾
3. Blood haemoglobin levels were measured by cyanmethemoglobin method using colorimeter.

4. BMI, was calculated using formula BMI=Weight in kilograms/(height in meters)².⁽⁹⁾

Statistical analysis: Statistical analysis was performed using the software SPSS version 23. Means of the different parameters were compared using one way analysis of variance (ANOVA). Pearson’s Correlations between serum ferritin, blood glucose and BMI were performed.

Results

Serum ferritin, fasting blood glucose levels, and BMI were compared between the three groups and correlations were made and tabulated in Tables 1 and 2 respectively.

Table 1: Means & Standard Deviations for Ferritin, Glucose and BMI among the 3 groups

Parameters	Group 1 (Healthy controls)	Group 2 (Pre-diabetes)	Group 3 (Diabetes)
Fasting Blood Glucose (mg/dl) **	90.24 ^a ± 5.66	122.60 ^b ± 19.69	168.57 ^c ± 39.44
Ferritin** (µg/l)	25.0 ^a ± 1.71	47.53 ^b ± 14.46	74.68 ^c ± 22.74
BMI*(kg/m2)	23.52 ^a ± 3.10	24.20 ^{a,b} ± 3.47	25.83 ^b ± 3.63

^{abcd}Mean bearing different superscript in a column differ significantly (NS- Non significant; *P<0.05; **P<0.01). For BMI: P=0.03 (groups 1 & 3)

Table 2: Correlations of Ferritin, Glucose and BMI among the 3 groups

	FBG	FERRITIN	BMI
FBG Pearson Correlation	1	.984**	.283**
Sig. (2-tailed)		.000	.007
Ferritin Pearson Correlation	.984**	1	.312**
Sig. (2-tailed)	.000		.003
BMI Pearson Correlation	.283**	.312**	1
Sig. (2-tailed)	.007	.003	

Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Obviously there was a significant increase in fasting blood glucose levels in the pre-diabetic and diabetic groups compared with the diabetic individuals. When the serum ferritin levels were analysed we found a highly significant (p<0.000) increase in its levels (74.68 ± 22.74µg/l) among the diabetic patients who formed the group 3, compared to those in group 1, who were normal and healthy (25.0 ± 1.71µg/l). Apart from this we noticed a sharp increase (p<0.000) in serum ferritin levels in pre-diabetics (47.53± 14.46µg/l) from that of the normal people and the rise was maintained between the pre-diabetics and the diabetics also (p<0.000). The individuals with type 2 diabetes had a higher BMI compared to the normal people as shown in table1 (p=0.03).

There is a high degree of correlation between serum ferritin and fasting blood glucose levels (p=0.000). There is also a significant correlation between serum ferritin and BMI (P=003) of individuals participating in the study. Fasting blood glucose levels also correlated with the BMI (P=0.007) of the participants.

Discussion

In our study, we have analyzed and compared the serum ferritin levels among the 3 groups (pre-diabetic and diabetic individuals and healthy people) and have related it with the fasting glucose levels.

Serum ferritin levels were found to be high in the pre-diabetic (P<0.000) and the rise was consistent with the group diagnosed to have diabetes mellitus Type 2 (P<0.000). Our finding correlates well with other studies, who have also found an increase in serum ferritin levels in type 2 diabetes mellitus.^(8,10,11,12,13) Positive correlation was found between serum ferritin and fasting insulin levels and it also was found to increase, with the duration of diabetes mellitus.^(8,12) Elizabeth Hughes et al have identified serum ferritin to be an important risk factor for glucose intolerance in Indian subcontinent.⁽¹³⁾ Hyperferritinemia have been found to be linked to insulin resistance and fatty liver in patients without iron overload also.⁽¹⁴⁾ Elevation in serum ferritin levels could be present even in the pre-diabetes stage of glucose impairment, long before the patient becomes diabetic.⁽¹⁵⁾

There is a positive correlation between serum ferritin and fasting plasma glucose levels in all the three groups. The increase in serum ferritin levels in the pre-diabetic and type 2 diabetic people compared to healthy ones, along with the existence of positive correlation between ferritin and glucose clearly suggests the strong link between iron metabolism and glucose homeostasis. BMI is also increased in glucose intolerant states like diabetes and pre-diabetes and there is some amount of correlation between ferritin and BMI. Similar associations between BMI and ferritin have also been reported by Gillum RF et al and Jose´ Manuel Fernandez et al.^(16,17)

Serum ferritin is considered to be a good reflection of the body iron stores in healthy people. Increased serum ferritin causes increased release of free iron, which in turn is responsible for generation of toxic free radicals like hydroxyl ions (Haber – Weiss reaction). The hydroxyl ions cause oxidation of proteins, peroxidation of membrane lipids and modification of nucleic acids which results in oxidative stress. Oxidative stress could promote phosphorylation at serine rather than tyrosine residues in the insulin receptors (during insulin action, normally tyrosine residues get phosphorylated) which results in Insulin resistance.⁽¹⁸⁾ Ferritin, is not only a source of free iron, but also an antioxidant.⁽¹⁹⁾ Its antioxidant activity is by binding to the excess free iron and hence reducing oxidative stress and its toxic manifestations.

Recent research indicates that there is often coexistence of subclinical inflammation in chronic diseases like Diabetes Mellitus. Serum ferritin, a marker of subclinical inflammation, may itself may be a risk factor for type 2 diabetes mellitus.⁽²⁰⁾ There is an increased oxidative stress as well as underlying subclinical inflammatory state, in diabetes mellitus. Ferritin is synthesized excessively in the body as a protective mechanism, as Ferritin has an antioxidant property and it is also a pro- inflammatory agent. Thus ferritin could either reflect excess body iron stores or inflammation which could have causative roles in diabetes. Some studies also suggest that increase in Ferritin level may also be due to leakage from hepatic cells.⁽¹⁴⁾ Excessive ferritin concentration can be a marker of iron overload and subclinical hemochromatosis in diabetes patients.⁽¹⁵⁾

Higher levels of ferritin were found to be associated with hyperinsulinemia and increased prevalence of the Metabolic Syndrome.^(21,22) Hepatic extraction and metabolism of insulin is reduced with increasing iron stores, leading to peripheral hyperinsulinemia.⁽²³⁾ In fact, the initial and most common abnormality seen in iron overload conditions is liver insulin resistance.⁽¹⁾ Diabetes status have been found to improve after phlebotomy.^(14,24)

In diabetes mellitus increased glycation of transferrin, decreases its ability to bind ferrous iron and hence there is an increased pool of free iron which in turn

stimulates increased synthesis of ferritin.⁽²⁵⁾ It is to be believed that increase in Ferritin synthesis results in internalization of Insulin receptors which contributes to Insulin resistance.^(15,17) Thus the glucose metabolism is found to be interlinked with iron metabolism and measuring serum ferritin levels as part of diabetic management, could aid in predicting the outcomes.

Conclusion

Serum ferritin levels positively correlated with the glycaemic status of the individuals, and are elevated in glucose intolerant states like pre-diabetes and diabetes mellitus type 2. This finding could have remarkable application in the diagnosis and management of diabetes mellitus. Serum ferritin could be used to predict an individual's tendency to develop diabetes mellitus and its complications like neuropathy, nephropathy, retinopathy and cardiovascular diseases. It could also help in assessing the prognosis of those presenting with pre-diabetes.

Serum ferritin could also be used as part of community based screening programmes to identify the high risk individuals, prone to develop diabetes in future. Measures to lower the serum ferritin levels and maintain it within the normal range, could reduce their paradoxical risk of developing diabetes and its related complications. Preventive measures like lifestyle modifications put forth to the high risk group presenting with high serum ferritin levels, might be an important step in reducing the morbidity and mortality, related to type 2 diabetes mellitus.

References

1. Dandona P, Hussain MA, Varghese Z, Politis D, Flynn DM & Hoffbrand AV. Insulin resistance and iron overload. *Annals of Clinical Biochemistry* 1983;20:77–79.
2. Piperno A. Classification and diagnosis of iron overload. *Haematologica* 1998;83:447–455.
3. C E Wrede, R Buettner, L C Bollheimer et al. 'Association between serum ferritin and the insulin resistance syndrome in a representative population'. *European Journal of Endocrinology*. 2006; vol 154:333-340.
4. Sumeet Smotra, R.P Kudyar. 'Relationship between Serum Ferritin and Type-2 Diabetes Mellitus'. *JK Science*. 2008 Oct-Dec; Vol 10:4.
5. Kevin Noel Keane, Vinicius Fernandes Cruzat et al. 'Molecular Events Linking Oxidative Stress and Inflammation to Insulin Resistance and beta cell Dysfunction'. *Oxidative Medicine and cellular longevity*; 2015 (2015):1-15.
6. Jeevan K Shetty, Mungli Prakash and Mohammad S Ibrahim. 'Relationship between free Iron and glycated Hemoglobin in uncontrolled type 2 Diabetes patients associated with complications'. *Indian Journal of Clinical Biochemistry*. 2008; Vol 23 (1):67-70.
7. Classification and Diagnosis of Diabetes *Diabetes Care* 2015;38(Suppl. 1):S8–S16.
8. Arul Senghor, N Bharathya, JS Kumar, Ebenezer William, Balasubramaniam. Serum Ferritin, Iron, TIBC, Hb in male patients with dysglycemia *Int J Biol Med Res*. 2012; 3(2):1609-1611.

9. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557–1565.
10. Boinapalli Sudakar, Shah Rita M and Yogesh Chand Yadav. Correlation of Serum Ferritin with Components of Metabolic Syndrome and its Relationship with the Insulin Resistance in Men and Women. *Clin Med Biochemistry* 2016; 2(1): 1-6.
11. Pramiladevi, Umakanth Boke, Shreeram Kora. 'Serum Ferritin Levels in Type II Diabetes Mellitus'. *Scholars Journal of Applied Medical Sciences*. 2013; vol 1(5):472-475.
12. Fulden Sarac, Sumru Savas, Sefa Sarac et al. 'Elevated Ferritin levels and the Relationship with Fasting Insulin Levels in Elderly Patients with Metabolic Syndrome'. *Journal of Diabetes Mellitus*.2014; vol 4(3):7.
13. Elizabeth A. Hughes, Jeetesh V. Patel, Zoisa Bredow et al. 'Ferritin as a Risk Factor for Glucose Intolerance amongst Men and Women Originating from the Indian Subcontinent'. *International Journal of Endocrinology*. 2015; vol 2015: 6.
14. Robert Brudevold, Torstein Hole, Jens Hammerstrom. 'Hyperferritinemia Is Associated with Insulin Resistance and Fatty Liver in Patients without Iron Overload'. 2008 October 28; *PLoS ONE* 3(10): e3547.
15. Faranak Sharifi, N. Mousavi Nasab, Zadeh HJ. 'Elevated Serum ferritin concentrations in prediabetic subjects'. *Diabetes and Vascular diseases Res*.2008 March; vol 5(1):15-8.
16. Gillum RF: Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men: the Third National Health and Nutrition Examination Survey. *Int J Obes Rel Metab Dis* 25:639–645, 2001.
17. Jose Manuel Fernandez-Real, Abel Lopez-Bermejo, and Wifredo Ricart. 'Cross-Talk between Iron Metabolism and Diabetes'. *Journal of Diabetes*. 2002 August; Vol 51:2348–2354.
18. Varman T. Samuel, Gerald I. Shulman. 'Integrating Mechanisms for Insulin Resistance: Common Threads and Missing Links'. *Cell*. 2012 March 2; Vol 148(5):852-871.
19. Fatmah A. Matough, Siti B. Budin et al. 'The Role of Oxidative Stress and Antioxidants in Diabetic Complications'. *Sultan Qaboos University Medical Journal*. 2012 Feb; Vol 12(1):5-18.
20. Helaine E. Resnick, Barbara V. Howard. 'Diabetes and Cardiovascular Disease'. *Annual Review of Medicine*. 2002 Feb; Vol 53:245-267.
21. Vari, I.S., Balkau, B., Kettaneh, et al. Ferritin and Transferrin Are Associated with Metabolic Syndrome Abnormalities and Their Change over Time in a General Population: Data from an Epidemiological Study on the insulin Resistance Syndrome (DESIR). *Diabetes Care*,2007; 30: 1795-1801.
22. Abril-Ulloa, V., Flores-Mateo, G., Solà-Alberich, R., Manuel-y-Keenoy, B. and Arija, V. Ferritin Levels and Risk of Metabolic Syndrome: Meta-Analysis of Observational Studies. *BMC Public Health* 2014; 14: 483.
23. Niederau C, Berger M, Stremmel W, Starke A, Strohmeyer G, Ebert R: Hyperinsulinemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation *Diabetologia*26:441–444, 1984.
24. Sundararaman Swaminathan, Vivian A. Fonseca et al. 'The Role of Iron in Diabetes and Its Complications'. *Diabetes care*.2007 July; Vol 30: 7.
25. Fujimoto S, Kawakami N, Ohara A: Non-enzymatic glycation of transferrin: decrease of Iron-binding capacity and increase of oxygen radical production. *Biol Pharm Bull* 18:396–400, 1995.