

## Serum ferritin level in type 2 diabetes mellitus - A case control study

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### Abstract

**Background:** Hyperferritinemia probably contributes insulin resistance and subsequently to decreased insulin secretion causes for development of insulin resistance.

**Objectives:** Compare HbA1c with Ferritin and find correlation between HbA1c and ferritin in type 2 diabetes mellitus patients, and also to find the best cut-off value for serum ferritin.

**Material and methods:** The study was conducted on type 2 diabetes mellitus patients attended the outpatient department. Totally 99 participants were enrolled for the study, out of which 49 were cases and 50 were age and sex controls. The FBS, PPBS, HbA1c and serum ferritin were estimated. Statistical package for social science software version 19.0 was used for statistical analysis.

**Results:** There statistically significant increase in all the biochemical parameters viz FBS, PPBS, HbA1c and serum ferritin levels in cases compared controls. The p value was 0.0001 for all the parameters, which is highly significant. There was a positive correlation between the HbA1c and Ferritin levels, but it was not statistically significant ( $r = 0.10$ ). The area under the ROC curve for serum ferritin values at various cut-off was 0.904 and the best cut-off of serum ferritin levels greater than 124ng/ml.

**Conclusion:** Serum ferritin levels were higher in type 2 Diabetes mellitus which positively correlated HbA1c. Thus, routine screening for serum ferritin concentration in diabetes patients can be done to assess the glyceemic control in type 2 DM.

**Key words:** Type 2 Diabetes Mellitus, Serum ferritin

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### Introduction

Diabetes mellitus (DM) consists a group of metabolic disorders that share common phenotype of hyperglycemia[1]. Diabetes is one of the most challenging health problems in 21<sup>st</sup> century[2]. In type-2 DM, insulin resistance is the primary event, followed by increasing degree of  $\beta$ -cell dysfunction[3]. Chronic, systemic subclinical inflammation has also been identified as a driving force for insulin resistance, metabolic syndrome, and type 2 DM [4]. The process of inflammation induces hepatic synthesis of various acute phase proteins such as serum ferritin which is believed to play a role in insulin resistance as well as atherosclerosis[5]. Higher incidence of type-2 diabetes mellitus (type 2 DM) has been observed with high levels of serum ferritin [6,7,8,9].

The etiopathogenesis of type 2 DM is multifactorial. Increased serum ferritin reflecting body iron overload, is often associated with, elevated blood

glucose and insulin levels are measures of insulin resistance [6,7,8,9]. Iron, could participate in the etiopathogenesis of T2DM [10]. Elevated iron stores may induce diabetes through various mechanisms including oxidative damage to pancreatic beta cells, impairment of hepatic insulin extraction by the liver and interference with insulin's ability to suppress hepatic glucose production. Long term microvascular and macrovascular complications of diabetes may be due to raised serum ferritin [6,7,8,9]. Iron is a transitional metal with strong pro-oxidant activity, leading to the production of reactive oxygen species that results in an increase in oxidative stress levels[11]. Ferritin synthesis is up-regulated by infection or inflammation, and cytokines such as IL-6 and IL-1 also induce the expression of ferritin[12]. Iron metabolism is regulated by hepcidin,. Under normal circumstances, hepcidin controls the efflux of iron from duodenal enterocytes and macrophages[10]. This process induces endocytosis and leads to the lysosomal degradation of the ferroportin transporter, where the level of released iron in the bloodstream is reduced[13]. Under chronic inflammatory conditions such as in T2DM, excessive cytokines such as IL-6 causes excessive production of hepcidin by directly stimulating the hepatocytes [14]. The probable role of ferritin as an iron overload marker in pancreatic damage or peripheral insulin resistance

results in hyper glycemia is not clear [15]. There is no much studies to show the best cut-off value for serum ferritin in type 2 DM.

Hence the present case control study was under taken to compare HbA1c, and Ferritin and find correlation between HbA1c and ferritin in type 2 diabetes mellitus (DM) patients, and also to find the best cut-off value for serum ferritin.

### Material and methods

The study was conducted on type 2 DM subjects attended the OPD at Hanagal Shri Kumareshwara hospital, Bagalkot. The study was approved by S.Nijalingappa Medical College ethical committee. Informed consent was obtained. The study was conducted from January 2012 to February 2013. The type 2 DM patients diagnosed on the basis of WHO criteria, irrespective of duration and treatment were selected for the study. Age and sex matched control were selected for the study.

Patients with diabetic complications, any infection, chronic renal failure, other systemic conditions, recent history of iron intake, history of repeated blood transfusion and hypertensive patients were excluded from the study. Pregnant women were also excluded from the study.

Under aseptic precautions 5 ml of fasting sample was collected. The fasting blood glucose (GOD, POD method) using semiautomated analyser Statfax 3300. The HbA1c was estimated by Nycocard reader method. The serum ferritin was estimated by chemiluminescence, kits supplied by Snibe Maglumini

using Maglumini 1000 instrument. PPBS was also estimated.

### Statistical analysis

Statistical package for social science (SPSS for window version; SPSS, 11.5 Inc, Chicago IL) software was used for statistical analysis. Pearson's correlation coefficient was used to show the correlation between the HbA1c and ferritin in DM. All the results were expressed as mean±SD.

### Results

Totally 99 participants were enrolled in the study, out of which 49 were cases and 50 were controls maximum age group was between 41-50 years (34%), followed by 51-60 years of age (31%). Gender wise distribution was 61 males and 38 females.

There was no significant difference in age between cases and controls. There was statistically significant increase in all the biochemical parameters viz FBS, PPBS, Hba1c and serum ferritin levels in cases compared controls. The p value was 0.0001 for all the parameters, which is highly significant (Table 1). There was a positive correlation between the HbA1c and Ferritin levels, but it was not statistically significant ( $r = 0.10$ ) (Figure 1). The area under the ROC curve for serum ferritin values at various cut-off was 0.904 (95% confidence interval, 0.828-0.954;  $p < 0.0001$ ) as shown in figure 2. Sensitivity and specificity of ferritin levels in diabetes at various cut-off values is shown in table 2. A maximum sensitivity of 93.88% and specificity of 80% were achieved in diabetes at the best cut-off of serum ferritin levels greater than 124ng/ml.

**Table 1: Biochemical parameters in cases and controls**

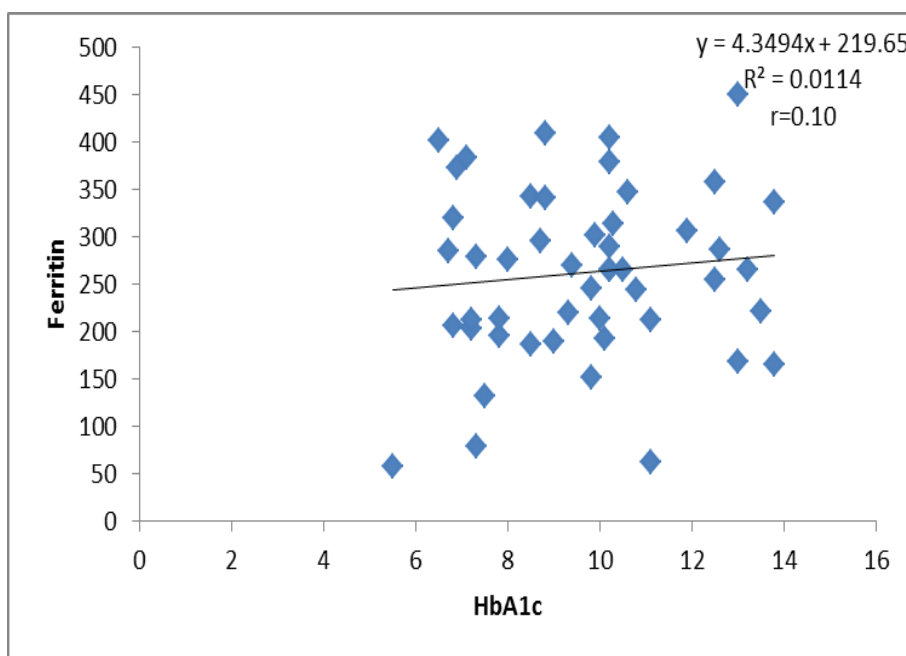
	Group	N	Mean±SD	t	P
Age in years	Cases	49	55.10±10.061	0.47	0.63 NS*
	Controls	50	56.02±9.213		
FBS mg/dl	Cases	49	202.39±89.786	8.734	0.0001 HS**
	Controls	50	90.85±9.608		
PPBS mg/dl	Cases	49	293.18±114.963	10.8	0.0001 HS**
	Controls	50	116.39±13.509		
HbA1c %	Cases	49	9.637±2.2024	12.680	0.0001 HS**
	Controls	50	5.514±.6547		
Ferritin	Cases	49	261.56±89.67109	9.557	0.0001 HS**
	Controls	50	99.5940±78.70429		

NS\*: Not significant, HS\*\*: Highly significant

FBS: Fasting blood sugar, PPBS: Post prandial blood sugar, HbA1c: Glycated Hemoglobin

**Table 2: Criterion values and coordinates of the ROC curve**

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>=19.6	100	92.7 - 100.0	0	0.0 - 7.1	1	
>56.8	100	92.7 - 100.0	38	24.7 - 52.8	1.61	0
>58.1	97.96	89.1 - 99.9	38	24.7 - 52.8	1.58	0.054
>59	97.96	89.1 - 99.9	40	26.4 - 54.8	1.63	0.051
>62.9	95.92	86.0 - 99.5	40	26.4 - 54.8	1.6	0.1
>74	95.92	86.0 - 99.5	54	39.3 - 68.2	2.09	0.076
>78.5	93.88	83.1 - 98.7	54	39.3 - 68.2	2.04	0.11
<b>&gt;124 *</b>	<b>93.88</b>	<b>83.1 - 98.7</b>	<b>80</b>	<b>66.3 - 90.0</b>	<b>4.69</b>	<b>0.077</b>
>132.1	91.84	80.4 - 97.7	80	66.3 - 90.0	4.59	0.1
>137	91.84	80.4 - 97.7	82	68.6 - 91.4	5.1	0.1
>168.1	85.71	72.8 - 94.1	82	68.6 - 91.4	4.76	0.17
>184	85.71	72.8 - 94.1	86	73.3 - 94.2	6.12	0.17
>189.3	81.63	68.0 - 91.2	86	73.3 - 94.2	5.83	0.21
>190	81.63	68.0 - 91.2	88	75.7 - 95.5	6.8	0.21
>192.4	79.59	65.7 - 89.8	88	75.7 - 95.5	6.63	0.23
>194	79.59	65.7 - 89.8	90	78.2 - 96.7	7.96	0.23
>245.9	57.14	42.2 - 71.2	90	78.2 - 96.7	5.71	0.48
>250	57.14	42.2 - 71.2	92	80.8 - 97.8	7.14	0.47
>254.3	55.1	40.2 - 69.3	92	80.8 - 97.8	6.89	0.49
>256	55.1	40.2 - 69.3	94	83.5 - 98.7	9.18	0.48
>265.3	46.94	32.5 - 61.7	94	83.5 - 98.7	7.82	0.56
>269	46.94	32.5 - 61.7	96	86.3 - 99.5	11.73	0.55
>284.3	38.78	25.2 - 53.8	96	86.3 - 99.5	9.69	0.64
>285	38.78	25.2 - 53.8	98	89.4 - 99.9	19.39	0.62
>382.8	8.16	2.3 - 19.6	98	89.4 - 99.9	4.08	0.94
>389	8.16	2.3 - 19.6	100	92.9 - 100.0		0.92
>450.2	0	0.0 - 7.3	100	92.9 - 100.0		1



**Fig. 1: Correlation between HbA1c and Ferritin.**

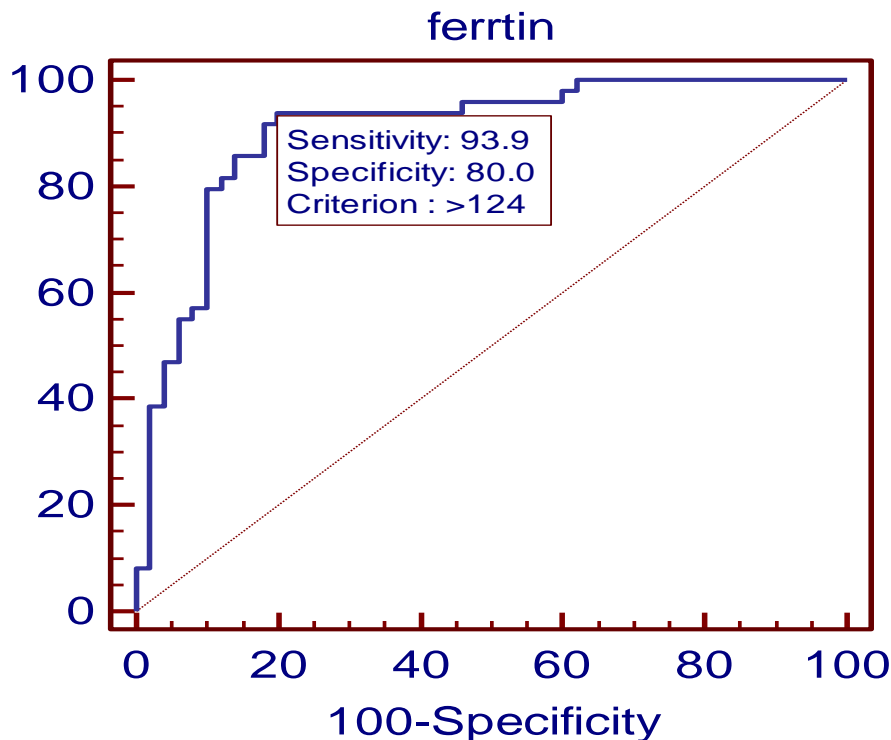


Fig. 2: ROC curve at various cut-off points for serum ferritin.

### Discussion

S Raj S and Rajan GV [7] showed significant higher levels of serum ferritin in diabetes than healthy controls and positive correlation between serum ferritin and HbA1c, our study is in accordance with this study, but we did not get statistically significant correlation between the serum ferritin and HbA1c.

Studies, have reported the possibility for a link between subclinical hemochromatosis and type 2 DM [16,17]. In some epidemiological studies serum ferritin was the second strongest determinant of blood glucose (next to BMI) in regression models and the third strongest determinant of serum insulin (next to BMI and age) [18]. In 1999 a survey by Ford et al in USA on 9486 diabetic patients find high levels of ferritin in diabetics [19]. Another study by Kwant [20] on the prevalence of C282Y mutation of hemochromatosis gene, determined the higher prevalence of this mutation in type 2 DM that could be an evidence for some relationship between these two disorders. Epidemiological studies reported a positive association between elevated ferritin levels and the risk of developing type 2 DM [20]. Others have determined ferritin just as a marker of pancreatic inflammation, and some have referred to it as a marker for insulin resistance [8]. Since insulin resistance has been considered as the basic factor in the pathogenesis of atherosclerosis [22] higher ferritin in atherosclerotic patients can be due to insulin resistance [8].

Fernandez in 1998 studied the relationship between serum ferritin and the results of glucose tolerance test

and insulin sensitivity in healthy subjects [23]. In this study the correlation between serum ferritin and diastolic blood pressure, HDL, glucose area under the curve and insulin sensitivity suggest that serum ferritin could be a marker of insulin resistance. Such results have also been reported by Kim et al. [18]. They suggest that serum ferritin may also be an independent determinant of poor metabolic control in diabetic patients [8]. The positive effect of ferritin reduction on blood glucose control was used for confirmation of the probable role of ferritin in DM pathogenesis but, the use of bloodletting may affect total hemoglobin level and HbA1c as well, so the use of HbA1c as a marker of blood glucose control has not been appropriate [8].

In the current study the best cut-off value for serum ferritin is 124 ng/ml, the study by Pramiladevi R. et al [6] in their study best cut-off value for serum ferritin was 140 ng/ml and area under curve was 0.626 and it was statistically significant.

Limitation of the study is that the small sample size, duration of diabetes, other iron parameters. Further studies are required with large sample size and optimal cut-off values so that these parameters can be used as glycemic control parameters or prognostic significance.

### Conclusion

Serum ferritin levels were higher in type 2 DM which positively correlated HbA1c. Thus, routine screening for serum ferritin concentration in diabetes patients can be done to assess the glycemic control in type 2 DM, with best cut-off value of 124 ng/ml.

**Conflict of Interest: None****Source of Support: Nil****References**

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