Original Research Article

# A study on relationship between serum ferritin and HbA1c in type 2 diabetes mellitus

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## Abstract

**Background & Objective:** To find the association of elevated serum ferritin levels with Type 2 Diabetes Mellitus and to study the relationship between serum ferritin levels and Hba1c in type 2 Diabetes mellitus. Our objective is to assess the serum ferritin levels in type 2 diabetes patients, to determine the role of serum ferritin level as an indicator of glycaemic control like HbA1c and also as a marker of insulin resistance. **Methods:** Physical examination and Laboratory investigation such as FBS, PLBS, Serum ferritin, HbA1c are done in every patient and collected detailed History. **Results**: Most common age groups are 51-60 years and 61-70 years, majority of study population comprised of males (69%), significant difference seen with gender wise and age wise distribution of Diabetes mellitus, mean values of HbA1c is 7.26%, FBS is 151.34 mg/dl, PPBS is 209.17 mg/dl and serum ferritin is 193.78 mg/dl. Correlation between duration of Diabetes and HbA1c with serum ferritin is statistically significant with p-value <0.001. With spearman correlation it is 1.0 with serum ferritin and HbA1c shows strong positive correlation. **Conclusion**: In our study we conclude that elevated levels of serum ferritin seen in patients with type 2 diabetes mellitus, Diabetic patients with increased HbA1c had significant hyperferritinemia and serum ferritin can be used as marker of glycaemic control as HbA1c and also a marker of insulin resistance in Diabetic patients.

**Keywords**: Type 2 Diabetes mellitus, Fasting blood sugar, postprandial blood sugar, serum ferritin, HbA1c, cardio vascular disease, cerebro vascular accident, oral glucose tolerance test, Antioxidant responsive element.



### Introduction

Diabetes is a metabolic disorder characterized by hyperglycaemia either due to insulin deficiency or insulin resistance[1]. People with diabetes develop characteristic microvascular complications like retinopathy, nephropathy, neuropathy, and macrovascular complications like coronary artery disease (CAD), cerebrovascular disease (CVA), peripheral vascular disease[2](PVD).

Complications due to diabetes are the major cause of disability, reduced quality of life, and death. Approximately 5.1 million people aged between 20 to 79 years of age died from diabetes accounting for 8.4% of the global mortality rate in the same age group[3]. In India, 65.1 million people in the age group of 20 to 79 years have diabetes (8.56%) and expected to rise to 109 million by the year 2035[4].

Serum Ferritin is an acute phase reactant and is a marker of iron stores in the body[5]. Iron is a transitional metal that can easily become oxidized and thus acts as an oxidant[6]. Elevated serum ferritin levels may induce diabetes through a variety of mechanisms that include: 1. Oxidative damage to pancreatic beta cells. 2. Impairment of hepatic insulin extraction by liver. 3. Interference with insulin ability to suppress gluconeogenesis and glycogenolysis[7].

Free radicals are formed disproportionately in diabetes due to glucose oxidation, non-enzymatic glycation of proteins, and oxidative degradation of glycated proteins. Higher levels of reactive oxygen species and associated decline of antioxidant defense mechanisms can lead to damage of subcellular organelles, increased lipid peroxidation, and the development of insulin resistance. Inflammation and oxidative stress can accelerate the process of atherosclerosis in diabetes mellitus.

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### Materials and methods

It is a Hospital based cross-sectional study conducted in 100 patients with Type 2 diabetes mellitus in medical wards of Sri Venkateswara Ramnarainaruia Government general Hospital, Tirupati. The duration of the study is one year from the date of approval by the institutional ethical committee (01/02/2020 – 31/01/2021). Study population were taken according to inclusion and exclusion criteria. For stats we used different non parametric tests such as Wilcoxon-Man-Whitney U test and Kruskal Wallis Test. For Parametric tests Chi-squared test, Fisher's exact test and Spearman correlation coefficient are used.

### Inclusion Criteria

Patients with Type 2 Diabetes Mellitus, Patients with age group 30 years and above and Patients who are willing to give valid informed written consent.

### Exclusion criteria

Patients with Type 1 Diabetes Mellitus, Patients who have Chronic Kidney Disease and Chronic Liver Disease. States associated with altered serum ferritin levels like Haemochromatosis, Chronic alcoholics, iron Deficiency anaemia, patients with repeated blood transfusions and chronic inflammatory states like Rheumatoid arthritis and SLE (Systemic Lupus Erythematous).

### Results

In this study, a total of 100 patients were enrolled after obtaining consent from the patients. The summary of basic clinical details of the study population is depicted in Table 1.

**Table-1: Summary of Basic clinical Details**

| Basic Clinical Details | Mean ± SD \|\| Median (IQR) \|\| Min-Max \|\| Frequency (%) |
|---|---|
| **Age (Years)** | 55.17 ± 12.13 \|\| 56.00 (45.00-64.00) \|\| 30.00 - 78.00 |
| **Age** | |
| 21-30 Years | 2 (2.0%) |
| 31-40 Years | 15 (15.0%) |
| 41-50 Years | 21 (21.0%) |
| 51-60 Years | 27 (27.0%) |
| 61-70 Years | 27 (27.0%) |
| 71-80 Years | 8 (8.0%) |
| **Gender** | |
| Male | 69 (69.0%) |
| Female | 31 (31.0%) |
| **Duration Of DM (Years)** | 4.70 ± 3.41 \|\| 3.50 (3.00-6.00) \|\| 1.00 - 18.00 |
| **Duration Of DM** | |
| ≤5 Years | 69 (69.0%) |
| 6-10 Years | 23 (23.0%) |
| >10 Years | 8 (8.0%) |

The above table summarises the following Mean values of basic clinical details for Age group is 55.17 ± 12.13 and Duration of DM is 4.70 ± 3.41. In this Males are more prominent to develop Diabetes mellitus which Comprised of 69% and less prominent in females which is 31% of 100 participants. Duration of Diabetes for which 69% participants had ≤5 Years, 23% had 6-10 years and 8% had >10 years.

Mean, median values for different biochemical parameters such as FBS, PPBS, HbA1c and Serum ferritin. Mean value for FBS is 151.34 ± 41.39 mg/dl, PPBS is 209.17 ± 58.86 mg/dl, HbA1c is 7.23 ± 1.69 % and for serum ferritin is 193.78 ± 74.99.

**Table-2: Distribution of participants in terms of serum ferritin**

| Serum Ferritin (ng/mL) | |
|---|---|
| Mean (SD) | 193.78 (74.99) |
| Median (IQR) | 188.45 (136.9-237.98) |
| Range | 82.3 - 446.5 |

Above tables describes the mean (SD) of serum ferritin (ng/mL) was 193.78 (74.99). The median (IQR) of serum ferritin (ng/mL) was 188.45. The serum ferritin (ng/mL) ranged from 82.3 - 446.5.

**Table 3: Association between Serum Ferritin and Gender (n = 100)**

| Gender | S. Ferritin | | | Chi-Squared Test | |
|---|---|---|---|---|---|
| | Normal | Abnormal | Total | $\chi 2$ | P-Value |
| Male | 44 (59.5%) | 25 (96.2%) | 69 (69.0%) | | |
| Female | 30 (40.5%) | 1 (3.8%) | 31 (31.0%) | | |
| Total | 74 (100.0%) | 26 (100.0%) | 100 (100.0%) | 12.111 | 0.001 |

Chi-squared test was used to explore the association between 'S. Ferritin' and 'Gender'. There was a significant difference between the various groups in terms of distribution of Gender ($\chi 2$ = 12.111, p = 0.001). In the group with the normal serum ferritin, 59.5% of the participants are males and 40.5% of the participants are females. In the group with the abnormal serum ferritin, 96.2% of the participants are males and 3.8% of the participants are females.

**Table 04: Association between HbA1c and duration Of DM (n = 100)**

| Duration Of DM | HbA1c | | | Chi-Squared Test | |
|---|---|---|---|---|---|
| | Normal | Abnormal | Total | $\chi 2$ | P-Value |
| ≤5 Years | 24 (100.0%) | 45 (59.2%) | 69 (69.0%) | | |
| 6-10 Years | 0 (0.0%) | 23 (30.3%) | 23 (23.0%) | | |
| >10 Years | 0 (0.0%) | 8 (10.5%) | 8 (8.0%) | 14.188 | 0.001 |
| Total | 24 (100.0%) | 76 (100.0%) | 100 (100.0%) | | |

A chi-squared test was used to explore the association between 'HbA1c' and 'Duration of DM'. There was a significant difference between the various groups in terms of distribution of duration of DM ($\chi 2$ = 14.188, p = 0.001).

To make group comparisons Wilcoxon-Mann-Whitney u test is used the mean (SD) of serum ferritin in patients with the normal HbA1c was 102.71 (13.34) and in the group with abnormal HbA1c was 222.53 (62.27) and it shows significant difference between the 2 groups in terms of serum ferritin (p = <0.001).

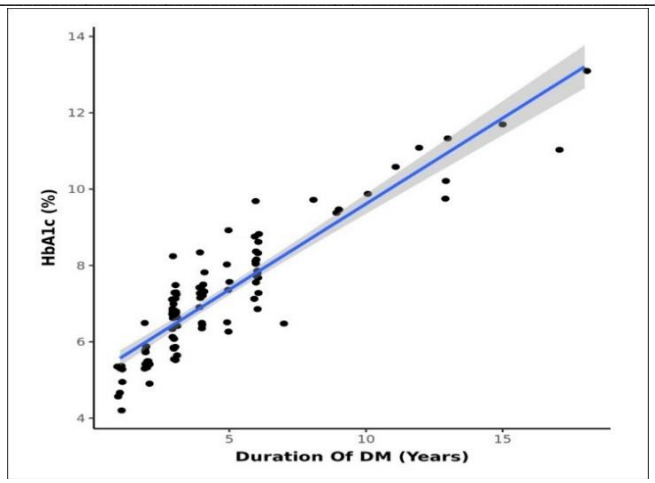


**Figure-1: Correlation between duration of diabetes and HbA1c**

The shaded grey area represents the 95% confidence interval of this trend line. There was a strong positive correlation between Duration of DM (Years) and HbA1c (%), and this correlation was statistically significant (rho = 0.88, p = <0.001).

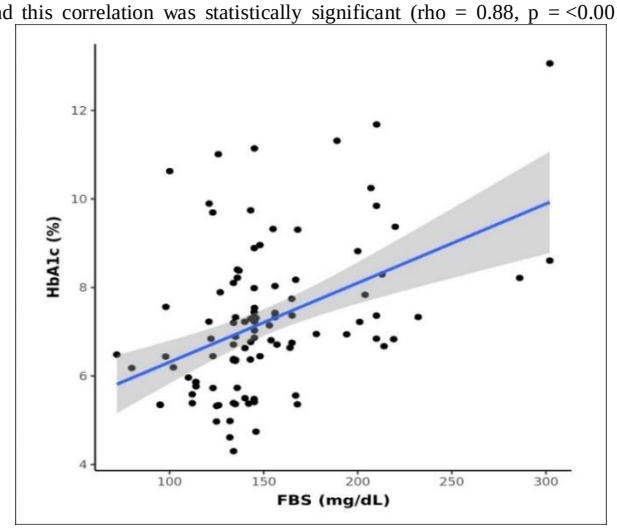


**Figure-2: Correlation between FBS and HbA1c**

The shaded grey area represents the 95% confidence interval of this trend line. There was a moderate positive correlation between FBS (mg/dL) and HbA1c (%), and this correlation was statistically significant (rho = 0.44, p = <0.001).

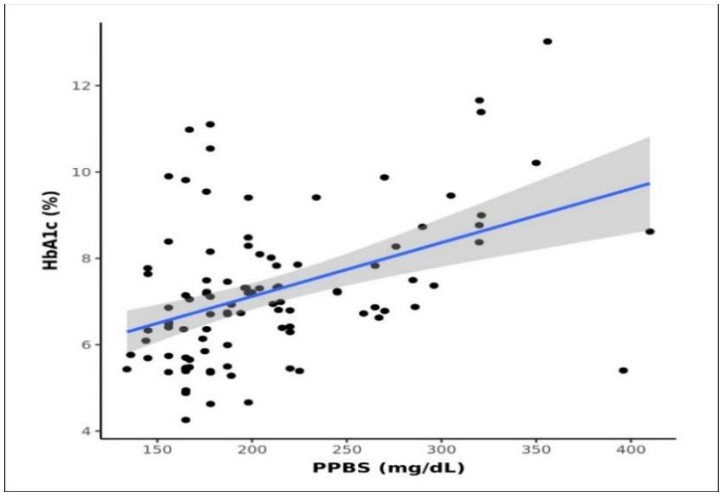


**Figure -3: Correlation between PPBS and HbA1c**

The shaded grey area represents the 95% confidence interval of this trend line. There was a moderate positive correlation between PPBS (mg/dL) and HbA1c (%), and this correlation was statistically significant (rho = 0.41, p = <0.001).

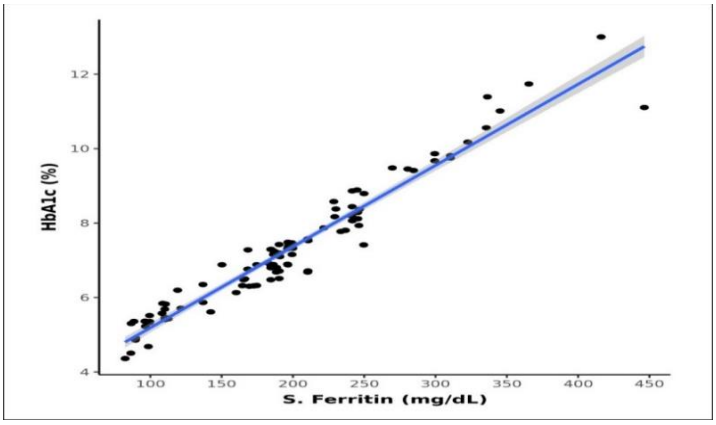


**Figure-4: Correlation between serum ferritin and HbA1c**

The shaded grey area represents the 95% confidence interval of this trend line. There was a very strong positive correlation between serum ferritin (ng/mL) and HbA1c (%), and this correlation was statistically significant (rho = 0.96, p = <0.001).

**Discussion**

Diabetes is a metabolic disorder characterized by hyperglycaemia either due to insulin deficiency or insulin resistance. Serum Ferritin, an acute phase reactant is a marker of iron stores in the body. Increased serum iron indicated by serum ferritin is thought to influence the development of type 2 diabetes. In chronic hyperglycaemic diabetic patients, the HbA1c fraction is abnormally elevated and it correlates positively with the glycaemic control.

The observation that the frequency of diabetes is increased in classic hereditary hemochromatosis[14] has derived evidence of systemic iron overload contributing to abnormal glucose.

Different theories have been suggested regarding the role of serum ferritin in type 2 diabetes, Ferritin has been considered as a marker of insulin resistance possibly due to iron deposition in the liver leading to hepatic insulin resistance and increased hepatic glucose production[15].

In the current study of 100 subjects, the mean ***age*** was 55.1 years and the median age was 56 years. The least age was 30 years, and the maximum age was 78 years, with a majority of subjects (27%) being in two age groups of 51-60 years and 61-70 years, followed by an age group of 41-50 years. When compared with similar studies by **Sharifi et al[8]. Khondker et al[9], Poonamarora[10], and Ramesh Chandra et al** shows statistically significant.

In the present study, most of the subjects were male (69%), and the rest were females accounting for 31%. The male predominance can be explained due to the higher proportion of male subjects attending the outpatient department than females it shows significant result when compared with similar studies conducted by **Poonamarora[10], Khondker et al[9] and Meghnaborah et al[12].**

Mean ***Duration of Diabetes Mellitus*** was 4.7 years and majority of subjects 69% are in the duration of < 5 years. In Male group it was 4.52 years and Females it was 5.10 years of duration. The subjects are divide into 2 groups' normal and abnormal groups for HbA1c and Mean duration of diabetes in normal HbA1c is 1.88 years and in abnormal 5.59 years.

For ***Blood glucose level*** in our present study mean FBS was 151.34 mg/dl and PPBS was 209.17 mg/dl. In male group mean FBS was 148.99 mg/dl and PPBS was 207.49 mg/dl where as in females mean FBS was 156.58 mg/dl and PPBS was 212.90 mg/dl when compared with other studies conducted by **Poonamarora[10], Ramesh Chandra et al[11]. and Meghnaborah et at[12].** the mean FBS was 189.8 mg/dl, 168 mg/dl and 156.2 mg/dl respectively shows no significant difference between the groups in terms of FBS (p-value 0.720) and PPBS (p-value 0.777).

The mean HbA1c in a well- controlled group is 5.6%, the moderately controlled group is 7.32% and the poorly controlled group is 10.0%. There was a significant difference between the 3 groups in terms of HbA1c with the median HbA1c highest in the poorly controlled group(>8.5%)In a study conducted by **Trivelli LA et al**[20]., in diabetic patients who had poor glycaemic control were found to have high values of HbA1c and observed that HbA1c was an indicator of glycaemic control.

The mean age in people with normal Hb1c was 54.38 years and the mean age in people with abnormal HbA1c was 55.42 years. When compared with other studies it shows weak positive correlation with the p-value 0.805.

Our study found that there was a strong positive correlation between the duration of diabetes and HbA1c and this correlation was statistically significant. (P-Value :< 0.001). Similar observations were found in studies conducted by **Meghnaborah et al[12]. and Narendrarawat et al[13].**

In our study, there was a moderate positive correlation between FBS and HbA1c and this correlation was statistically significant (p-value: <0.001) and similarly moderate positive correlation was found between PPBS and HbA1c and this correlation was statistically significant (p-value :< 0.001). A similar observation was found in the study conducted by **Mayor B Davidson et al[17]**, the paired values of fasting plasma glucose and HbA1c or fasting plasma glucose and fructosamine values together predict the likelihood of having diabetes in high-risk subjects and could replace the time consuming and laborious 2-hour oral glucose tolerance test in the diagnosis of diabetes.

Serum ferritin, a marker of iron stores in the body was significantly higher in diabetic patients, and ferritin is significantly increased as the duration of diabetes is increased. On measuring serum ferritin levels in 100 diabetic patients in our study, it was found that the mean serum ferritin was 193.78 ng/ml. A study done by **Kim et al[18].** in Korea University Hospital showed that serum ferritin levels were high in type 2 diabetes patients than in the controls. They concluded that serum ferritin can be used as a marker of insulin resistance in type 2 diabetic patients.

Mean serum ferritin is maximum in the age group of 61- 70 years with the value of 208.4 ng/mL followed by 51-60 years with a value of 195.2 ng/mL and least in the age group of 21-30 years with a value of 109.4 ng/mL. With spearman correlation it showed weak positive correlation.

In our study mean serum ferritin in the male group was 193.29

ng/mL and in the female group was 194.85 ng/mL. There was no statistical significance between the two groups in terms of serum ferritin (p-value: 0.952).On comparing the elevated levels of serum ferritin with the duration of diabetes, it was found that there was a strong positive correlation between the duration of diabetes and serum ferritin and this correlation was statistically significant ( p-value :<0.001). Similar observations were made by studies conducted by **Ramesh Chandra et al[11], Narendra rawat et[13]. And Poonam arora[10].**The mean serum ferritin levels in the people with normal FBS was 164.92 ng/mL and in the people with abnormal FBS was 196.63 ng/mL. Serum ferritin had a positive correlation with HbA1c and FBS. This reflects the relation between serum ferritin and glycaemic control both short term and long term. **Cantur KZ et al[19].** in their studies noticed high ferritin levels in diabetic patients with poor glycaemic control. Correlation between ferritin level and diabetic retinopathy is also found in their study[20].The mean of serum ferritin in patients with normal HbA1c was 102.71 ng/mL and in patients with abnormal HbA1c was 222.53 ng/mL. There was a significant difference between the two groups in terms of serum ferritin (p = <0.001), with the mean serum ferritin being the highest in the group of patients with abnormal HbA1c. There was a strong positive correlation between serum ferritin and HbA1c and this correlation was statistically significant. The p-value of <0.001 obtained indicates that both the parameters have a high statistical significance. Spearman correlation was used to explore the correlation between the two variables and the spearman correlation coefficient which is obtained is 1.0 which indicates a strong positive correlation[20-23].In a study conducted by **Ramesh Chandra et al[11].** on 100 diabetic patients, serum ferritin was significantly higher in diabetics and serum ferritin had a positive correlation with increasing duration of diabetes and glycated haemoglobin. It supports the above finding of serum ferritin correlation with HbA1c.

**Conclusion**

After reviewing the significant findings from our study and we concluded that there is Elevated levels of serum ferritin in patients with Type 2 Diabetes Mellitus, patients with Diabetes Mellitus and in increased HbA1c had significant hyperferritinemia and serum ferritin can used as a marker of glycaemic control as HbA1c and also used as a marker of insulin resistance in Type 2 Diabetes mellitus patients.

**Institutional Review Board Statement**

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Sri Venkateswara Medical College, Tirupati (protocol code 02/2020 and Date of approval was 01/02/2020).

**References**


1. Valdez R, Liu T, Yoon PW, Khoury MJ. Family history and prevalence of diabetes in the U.S. population. Diabetes Care 2007 30: 2517-22.
2. Thilip Kumar G, Saravanan A, Ramachandran C, and John Nitin Ashok. Mean blood glucose level and glycated haemoglobin level in patients of non- insulin dependent diabetes mellitus and its correlation with serum ferritin level. Int J Med Sci 2011; 4 (1& 2): 13-17.
3. Roglic G, Unwin N. Mortality attributable to diabetes: estimates for the year 2010. Diabetes Res ClinPract 2010; 87(1): 15-19.
4. IDF Diabetes Atlas, 2013; 6th edn. Chapter-2.1;34.
5. Koorts AM, Viljoen M. Acute phase proteins: Ferritin and ferritin isoforms. University of Pretoria, South Africa 2011; 154-84.
6. Herbert V, Spencer S, Jayatilleke E, Kasadan T. Most free radical Injury is iron-related: Itis promoted by iron, heme, holoferritin, and vitamin C and inhibited by deferoxamine and apoferritin. Stem Cells 1994; 12: 289-303.
7. Gallou G, Guilhem I, Poirier JY, Ruelland A, Legras B, Cloarec L. Increased serum ferritin in insulin-dependent diabetes mellitus: relation to glycemic control. ClinChem 1994; 40: 947-8.
8. Khondker F. et al. Relationship between serum ferritin level and HbA1c in Bangladeshi type 2 diabetic patients. AKMMCJ 2008;26(2):77-82.
9. Arora P. Correlation between Serum Ferritin and Glycated Hemoglobin Level in patients of Type 2 Diabetes Mellitus. IJCRR 2017; 9(6):30-33.
10. Ramesh Chandra et al. Level of Serum Ferritin and Glycated hemoglobin in type 2 diabetes patients. International Journal of Medicine and Health Research 2016; 2(2): 49-51.
11. Bo-Wei-liu et al. The Relationship between Serum Ferritin and Insulin Resistance in Different Glucose Metabolism in Nonobese Han Adults. International journal of endocrinology 2015; 6(11): 521-525.
12. Fernandez-Real JM, Lopez-Bermejo A, Ricart W. Iron stores, blood donation, and insulin sensitivity and secretion. *Clin Chem* 2005;51:1201–1205
13. Sharifi F and Sazandeh Sh. Serum ferritin in type2 diabetes mellitus and its relationship with HbA1c. Acta Med Iranica 2004; 42(2): 142-45.
14. Mayor Davidson B., David Schriger, Anne Peters L., et al., 1999 " Relationship between fasting blood glucose and glycosylated hemoglobin". JAMA, 281(13):1203-1210.
15. Herbert V. Everyone should be tested for iron disorders. J Am Diet Assoc 1992; 92: 1509-76.
16. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores with risk of type 2 diabetes in apparently healthy women. JAMA 2004; 291:711-7.
17. Cantur KZ, Cetinarslay B, Tarkun I, Canturk NZ. Serum ferritin levels in poorly- and well-controlled diabetes mellitus. Endocr Res 2003; 29:299-306.
18. Eschwege E, Saddi R, Wacjman H, Levy R, Thibult N, Duchateau A. HbAIc in patients on venesection therapy for hemochromatosis. *Diabetes Metab* 1982; 8: 137-40.
19. American Diabetes Association. Standards of medical care in diabetes-2010. Diabetes Care2010;33:S11-S61.
20. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. Biochim Biophys Acta1996;1275:161-203.
21. Fernandez Real JM, Penarroja G, Castro A, et al. Bloodletting in high-ferritin type 2 diabetes: effects on insulin sensitivity and β-cell function. Diabetes 2002;51:1000- 1004.
22. Konijn AM, Hershko C. Ferritin synthesis in inflammation: Pathogenesis of impaired iron release. Br J Hematol1977;37(1):7-16.
23. Chasteen ND. Ferritin: uptake, storage, and release of iron. Met Ions BiolSyst 1998;35:479-51.


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