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Research Article

STUDY OF SERUM FERRITIN AND GLYCEMIC CONTROL IN MALES WITH TYPE 2 DIABETES MELLITUS

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A B S T R A C T

Background: Ferritin is a ubiquitous intracellular protein that reflects body iron stores. It is also a positive acute phase protein and a marker of inflammation. Increased body iron stores have been associated with the development of glucose intolerance, type 2 diabetes, and gestational diabetes. The present study is carried out to find the association of serum ferritin with fasting blood sugar (FBS) and HbA1c in type 2 diabetic males, and to study the influence of body iron stores on glycaemic control.
Methods: The study included 40 male patients between 25 to 60 years of age, suffering from type 2 diabetes of less than 10 years duration. Serum ferritin was estimated by ELISA kit method, while fasting blood sugar (FBS), haemoglobin (Hb) and HbA1c were estimated by automated method.
Results: High frequency of raised serum ferritin was observed, even though haemoglobin levels were within physiological
limits.HbA1c ($p=<0.0001$) and FBS ($p=0.026$) were found to have significant association with serum ferritin levels, and the correlation between serum ferritin and HbA1c was strongly positive ($r=0.751$, $p<0.0001$).
Conclusions: There is a significant association between elevated iron stores measured by serum ferritin levels and type 2 diabetes mellitus. Patients of type 2 diabetes with increased level of serum ferritin had poor glycaemic control reflected by increased levels of HbA1c.

INTRODUCTION

Diabetes Mellitus (DM) is a group of common metabolic disorders that share the phenotype of hyperglycaemia. Various factors which can contribute to hyperglycaemia include reduced insulin secretion, decreased glucose utilization and increased glucose production (Powers *et al*, 2005). Type 2 diabetes is increasing in frequency globally. The worldwide spread of diabetes among general population is estimated to increase to 300 million in 2025 (Ghazanfari *et al*, 2010; Adeghate *et al*, 2006). Chronic hyperglycaemia causes increased glycation of protein including haemoglobin resulting in the formation of Advanced Glycated End products (AGE) (Singh *et al*, 2014).Measurement of glycated proteins primarily HbA1c (glycated haemoglobin) is effective in monitoring long-term glucose control in people with diabetes mellitus (David, 2012). Ferritin is ubiquitous, highly conserved iron-binding protein, and has been known as an index of body iron stores. Ferritin is proven acute phase protein and is considered as an inflammatory marker.

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In oxidative stress, Fe^{2+} enters the cells and then oxidised to Fe^{3+}, linked to ferritin and as a result protects cells from oxidative stress (Theil, 1987). Increasing concentration of iron and ferritin in cells can lead to insulin resistance and dysfunction of β cells of pancreas. Hyperinsulinemia due to resistance to insulin may hence be regarded as responsible factor or increased serum ferritin (Jehn *et al*, 2004; Ashourpour *et al*, 2010). Several studies have found high serum ferritin levels in type 2 diabetic patients and it has been shown that lowering the elevated serum ferritin levels correlated well with diabetes control and improved fasting blood glucose and glycated hemoglobin (Cutler, 1998).Serum ferritin has been considered as a component of insulin resistance syndrome (Fernandez-Real *et al*, 1998).

Increased ferritin may induce diabetes through a variety of 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 (Raj and Rajan, 2013).

The present study has been carried out to find the association of serum ferritin with fasting blood sugar (FBS) and HbA1c in

type 2 diabetic males, and to study the influence of body iron stores on glycaemic control in diabetes.

MATERIAL AND METHODS

The study population consisted of 40 clinically diagnosed uncomplicated type 2 diabetic male patients between 25 to 60 years of age with duration of diabetes less than 10 years. An informed consent was taken from the patients before the collection of samples. The ethical clearance was obtained from the Ethical Review Board of the institution. Patients on insulin therapy or with known associated complications such as anaemia, cardiovascular disease, nephropathy, retinopathy or any other macrovascularcomplications were excluded from the study. The personal information, physical characteristics, and other relevant information of the patients were obtained.

About 3 ml of venous blood sample was collected from each subject after overnight fasting. Fasting blood sugar (FBS), haemoglobin (Hb), HbA1c, and serum ferritin levels were estimated in each sample. Serum ferritin was estimated by principle of solid phase sandwich ELISA (Double sandwich ELISA), using DRG® Human Ferritin ELISA Kit (Cat. No. EIA 4292), DRG International™, Inc., USA (Intra assay CV 5.0% and Inter-assay CV 5.9%).while fasting blood sugar (FBS) and HbA1c were estimated by automated method using Roche Cobas® 6000, Roche Diagnostics ™ USA, as per manufacturer's protocol. Haemoglobin was estimated by cyanide free sodium lauryl sulphate method.

Statistical analysis: Data was expressed as percentage and mean ± S.D., Kolmogorove-Smirnove analysis was performed for checking linearity of the data. Student 't' test (two tailed, independent) and Chi-squaretest/Fisher's exact test has been used to find out the association between various study parameters. P value <0.05 was considered as statistically significant. Pearson's Correlation analysis was performed to assess correlation between two quantitative parameters. SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007, Microsoft® Inc USA was used perform the statistical analysis.

RESULTS

Table 1 shows general characteristics of the study subjects. Out of 40 subjects in total, 24 (60.0%) belonged to age group ≤ 50 years and 16 (40.0%) subjects were above 50 years of age. Duration of diabetes in 30 (75.0%) subjects was ≤ 5 years while in 10 (40.0%) subjects, it was noted to be >5 years. Body Mass Index (BMI) of the subjects showed that 25 (62.5%) were under obese I category. This was followed by 9 (22.5%) subjects in overweight category. 3 (7.5%) subjects were found to be underweight while, 3 (7.5%) subjects were found to have BMI>30 kg/m^{2}hence were under obese II category. HbA1c was found to be >9% in 27 (67.5%) subjects while ≤9% in 13 (32.5%) subjects. Ferritin level was found to be >300ng/ml in 27 (67.5%) subjects while, 13 (32.5%) subjects had normal ferritin levels.

Table 1 General characteristics in study subjects

Characteristics		Frequency	Percent
Age (years)	</=50	24	60.0
	>50	16	40.0
Duration (years)	</=5	30	75.0
	>5	10	40.0
BMI (kg/m^2)	18.5-22.9	3	7.5
	23-24.9	9	22.5
	25-29.9	25	62.5
	>30	3	7.5
HbA1c (%)	</=9	13	32.5
	>9	27	67.5
Ferritin (ng/ml)	12-300	13	32.5
	>300	27	67.5

Table 2 shows descriptive statistics of various parameters in study subjects. No significant association of ferritin levels was noted with age, duration of diabetes, BMI, and Hb, HbA1c (p=<0.0001) and FBS (p=0.026) were found to have significant association with ferritin levels, indicating higher HbA1c and FBS in subjects with high Ferritin levels.

Table 2 Descriptive statistics of various parameters in study subjects

	Ferritin (ng/ml)	N	Mean	S.D.	S.E.	t	P value
Age(Yrs)	12-300	13	49.38	7.88	2.19	1.126	.270
	>300	27	46.26	8.88	1.71		
Duration (yrs)	12-300	13	3.85	1.72	0.48	-.782	.441
	>300	27	4.33	2.08	0.40		
BMI(kg/m2)	12-300	13	26.32	2.34	0.65	-.022	.982
	>300	27	26.34	2.51	0.48		
HbA1c (%)	12-300	13	8.52	0.76	0.21	-6.584	<.0001
	>300	27	10.64	1.26	0.24		
FBS (mg/dl)	12-300	13	153.31	24.13	6.69	-2.315	.026
	>300	27	193.85	60.53	11.65		
Hb(g%)	12-300	13	14.16	0.99	0.28	-1.414	.171
	>300	27	14.63	0.93	0.18		

The Pearson correlation of ferritin with age, duration of diabetes, BMI, HbA1c, FBS and Hb is shown in Table 3. In the present study, a significant strong positive uphill correlation is observed between serum ferritin and HbA1c levels (Fig.1). The correlations of serum ferritin with age, duration of diabetes, BMI, FBS and Hb in diabetics was not found to be significant.

Table 3 Pearson Correlation between Ferritin and various parameters

	Parameters	r	P value
Ferritin (ng/ml)	Age (yrs)	-0.199	0.217
	Duration (yrs)	-0.006	0.971
	BMI (kg/m^2)	0.037	0.821
	HbA1c (%)	0.751	<0.0001
	FBS (mg/dl)	0.308	0.054
	Hb (g%)	0.226	0.162

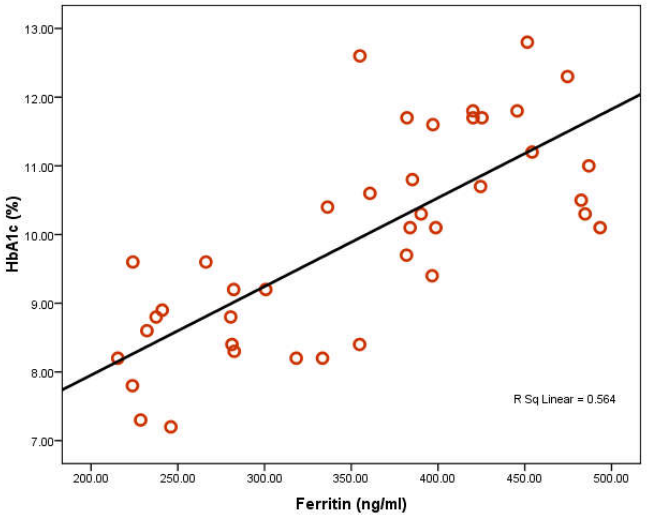

Fig 1 Scattered plot of HbA1c with respect to Ferritin

DISCUSSION

Diabetes mellitus is associated with low-grade inflammation as reflected by increase in inflammatory markers. Persistent

hyperglycaemia in uncontrolled diabetics cancause inflammation and increased oxidative stress from glucose auto-oxidation can lead to detrimental consequences. Long-standing hyperglycaemia can lead to the formation of Advanced Glycation End products (AGE) which plays an important role in the pathogenesis of diabetes complications including nephropathy, retinopathy and neuropathy. AGEs causes tissue damage by forming cross-linking various structural and functional proteins including plasma proteins and collagen. Thus, complications in type 2 diabetes are dependent on long-term glycaemic control (Fernandez-Real *et al*, 2002a).

In present study it was observed that levels of HbA1c, FBS and serum ferratin were significantly higher in study subjects. Similar findings were observed by Chandrashekhar *et al* and Kundu *et al* (Chandrashekhar *et al*, 2014; Kundu *et al*, 2013). We observed no significance association between higher ferritin levels and BMI in study subjects. While, Chandrashekhar *et al*, Kundu *et al* and El-Halim and El-Hadidy observed significantly higher increase of BMI in diabetic subjects (Chandrashekhar *et al*, 2014; Kundu *et al*, 2013; (El-Halim and El-Hadidy, 2016).

Serum ferritin generally considered as an index of body iron stores, is also a potent inflammatory marker (Rambod, 2008). Kalantar-Zadeh *et al* have reported elevated levels of serum ferritin indiabetes mellitus due to inflammation, independent of iron stores (Kalantar-Zadeh *et al*, 2004). Sharifi and Sazandeh reported that serum ferritin levels are increased in type 2 diabetes mellitus (Sharifi and Sazandeh, 2004). Kaye *et al* have reported elevated serum ferritin level as a risk factor for type 2 diabetes mellitus with iron overload (Kaye *et al*, 1993).

Increased ferritin levels can cause pancreatic beta-cell dysfunction and increased insulin resistance, thereby leading to diabetes mellitus. Increased accumulation of iron affects insulin synthesis and its secretion from the pancreas and interferes with the insulin-extracting capacity of the liver. Iron deposition in muscle decreases glucose uptake because of muscle damage. Conversely, insulin stimulates cellular iron uptake through increased transferrin receptor externalization. Thus, insulin and iron can mutually potentiate their effects leading after a vicious cycle to insulin resistance and diabetes (Fernandez-Real *et al*, 2002b).

Only males were included in our study to rule out other confounding factors for increased ironturnover under physiological conditions. Haemoglobin levels were within physiological range which excluded other haematological causes for iron overload. In our study, serum ferritin levels were positively correlated with HbA1c in type 2 diabetes ($r=0.751$, $p<0.0001$). Very high levels of serum ferritin were observed in cases with poor glycaemic control. Similar results were reported by Shetty J K *et al* that diabetics with increased level of serum ferritin had significantly poor glycaemic control reflected by higher levels of glycated haemoglobin (Shetty *et al*, 2008). According to Eschwege E *et al* apositive correlation between increased serum ferritin and poor glycaemic control, reflected by higher HbA1cwas observed (Eschwege *et al*, 1982).

Studies have shown that short term improvement in glycaemic control is followed by variable decreases in serum ferritin concentration (Fernandez-Real *et al*, 1998). Dymock *et al* showed that increased serum ferritin levels are associated with increased serum insulin levels reflecting insulin resistance, poor glycaemic control and complications of type 2 diabetes (Dymock *et al*, 1972). According to Borah and Goswami, strong positive correlation was found between HbA1c% and serum ferritin levels and the correlation was found to be statistically significant ($p<0.01$) (Borah and Goswami 2016). On the contrary, Sharifi and Sazandeh observed no correlation between serum ferritin and glycaemic control in diabetes (Sharifi and Sazandeh, 2004).

In our study no correlation between ferritin levels and FBS levels was observed. On contrary, El-Halim and El-Hadidy stated positive significant correlation between these parameters (El-Halim and El-Hadidy, 2016).

Positive correlation between serum ferritin and HbA1c indicates hyperglycaemia causing increased glycation of haemoglobin and increased release of free iron from glycated proteins like haemoglobin, thus increasing the level of ferritin. This increased presence of iron pool will enhance oxidant generation leading to damage to biomolecules (Shetty *et al*, 2008). Findings of Borah and Goswami *et al* indicated that serum ferritin was increased in diabetes as long as glycemic control was not achieved and that this increase may contribute to the pathogenesis of this disease as well as in the development of complications. Thus, routine screening for serum ferritin concentration in pre-diabetes and diabetic patients can be done to assess the body iron stores (Borah and Goswami 2016).

CONCLUSION

Increased ferritin levels may be one of the causes or result of development of insulin resistance, diabetes mellitus and its complications. The findings of our study suggest that iron overload reflected by increased serum ferritin level is positively related to poor glycaemic control. Estimation of serum ferritin may be a useful tool in screening diabetics with poor glycaemic control who are at increased risk of developing diabetes complications.

Declarations

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Ethical approval: Yes

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