ORIGINAL ARTICLE

Relationship between Serum Ferritin and Type-2 Diabetes Mellitus

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Abstract

To find out the relationship between serum ferritin (SF) & serum insulin (SI) levels in type-2 DM and to study the influence of body iron stores on various biochemical parameters and diabetic complications. Settings and Design: Postgraduate Department of Medicine in tertiary care hospital in North India. Observational study. A total of 50 obese type-2 diabetic patients were selected randomly and were compared with an equal number of age, sex, BMI matched controls to find out co-relation between SF and SI levels. Influence of body iron stores on various biochemical parameters like Hb(A1c), total cholesterol(TC),Triglyceride(TG), high density lipoprotein (HDL), uric acid (UA) and low density lipoprotein (LDL) as well as development on diabetic complications was also studied.A directly proportional relationship was found between SF and SI levels. The correlation between SF and SI was significant. Diabetics with increased level of SF had significantly poor glycemic control reflected by higher levels of Hb(A1c). Significant relationship was found between increased SF and increased TC, TG and UA except LDL levels in diabetic patients and with decreased serum HDL levels. A similar relationship was evident between increased SF and nephropathy, retinopathy neuropathy and hypertension, where as, there was non significant relationship found between increased SF and peripheral vascular disease and ischemic heart disease.It is clear from the present study that increased SF levels are associated with increased SI levels reflecting insulin resistance, poor glycemic control and complications of type-2 DM

Key words

Serum Ferritin, Diabetes Mellitus, Insulin Resistance

Introduction

It is recognized recently that, increased body iron stores are associated with the development of glucose intolerance, gestational diabetes, type-2 DM and insulin resistance syndrome (1-5). Frequent blood donation lead to decrease iron stores, which in turn reduces postprandal hyperinsulinemia and improves insulin sensitivity (6). Phlebotomy is followed by drop in serum glucose, cholesterol, triglycerides and improvement in both beta cell secretion and peripheral insulin action in type-2 DM (7, 8). Epidemiological studies also indicate the same correlation (9, 10). Poorly controlled patients of DM have hyperferritinemia which co-relates with diabetic retinopathy, diabetic nephropathy and vascular dysfunction (11- 13).

It is important to realize that raised levels of iron above physiological requirement serve no useful purpose in DM patients. Although few indirect evidences from the western region exist suggesting that iron overload influences DM in a negative way, but overall there is paucity of literature especially from India showing direct evidence that there is difficult control of DM in patients with iron overload. Moreover, finding out such correlation in Indian population carry great clinical significance as anemia in very prevalent in Indian population and continuous efforts are being made at physician, community and Government level to prevent and treat anemia which can influence the coexisting diabetic state. Hence, the present preliminary, direct and comprehensive study was

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planned to find out the relationship between serum ferritin (SF) & serum insulin (SI) levels in type-2 DM and to study the influence of body iron stores reflected by SF on various biochemical parameters and diabetic complications in an Indian population.

Material and Methods

The present observational study was conducted from June 2004 to May 2005. Ethical clearance from local review board and informed consents from patients/control was taken. A total of 50 obese type-2 diabetic patients were selected randomly according to a block permuted randomization plan. These patients were compared with an equal number of age, sex, BMI matched controls selected randomly to find out co-relation between SF (pathozyme ferritin EIA method) and SI (RIA method) levels. To find out the influence of body iron stores on various biochemical parameters diabetics underwent the following investigations: SF levels, fasting, postprandal and random blood glucose, lipid profile, glycosylated Hb levels and uric acid (UA) using standard methods.To find out the influence of body iron stores on various complications in DM patients were evaluated for diabetic complications like Diabetic Retinopathy, Diabetic Nephropathy, Coronary Artery Disease, Diabetic Neuropathy, Cerebrovascular Disease, Perpheral Vascular Disease and correlation was studied with increased SF levels.

Statistical Analysis

Data collected during the study was analyzed using statistical software Epi-info version 6. Co-relation between SF and SI in patients and controls was evaluated using Pearson Product Moment Co-relation Co-efficient. Chi Square test was used in analyzing the influence of body iron stores on biochemical parameters and diabetic complications. All tests were considered statistically significant if the p-value was <0.05.

Results

Present study was done on 50 type-2 obese diabetic patients i.e. 22 males & 28 females with varying duration of illness (Table-1). A directly proportional relationship was found between SF and SI levels. The correlation between SF and SI is found to be statistically significant (r= .772, P .01, two tailed). The levels of SF were found higher in 72% of the 50 type-2 diabetic patients as compared to 20% in the controls. Similarly levels of SI were found to be higher in the 50 type-2 diabetic patients i.e. in 70% as compared to 34% in controls (Table-2).

Relationship Between SF & Biochemical Parameters in Diabetic Patients *(Table-3)*

The association between poor glycemic control and increased SF levels was found to be significant as compared to those with glycemic controls. It was found that those with increased level of SF, more number of patients had poor glycemic control reflected by higher levels of Hb (A1c) as compared to those with normal levels and was found to be statistically significant ($p < 0.05$).

67% of the 50 type-2 diabetic patients with increased SF levels had increased total cholesterol (TC) as compared to 26% of those with normal SF levels. This was found to be significant ($p < 0.05$). Out of 50 patients, significant ($p < 0.05$) ie.77% had increased serum triglycerides (TG) in association with increased SF as compared to 42% of those with normal SF levels.

Out of 50 patients, 48% had decreased high density lipoprotein (HDL) in association with increased SF as compared to 10.5% of those with normal SF levels. It was found that those with increased level of SF, more number of patients had decreased HDL and was found to be significant ($p < 0.05$). It was found that those with increased SF more number of patients had higher levels of serum uric acid (UA) as compared to controls and was found to be significant ($p<0.05$). Out of 50 patients, 45% had increased low density lipoprotein (LDL) in association with increased SF as compared to 10.5% of those with normal SF levels. There was non significant relationship found between increased SF and increased LDL levels in diabetic patients (p-0.08).

Relationship Between SF & Complications in Diabetic Patients *(Table-4)*

Out of the 50 type-2 diabetic patients 71% of the patients with the increased SF had nephropathy and retinopathy respectively as compared to 26% of those with normal SF levels. This was found to be significant ($p < 0.05$). 70% of the 50 type-2 diabetic patients had neuropathy and increased SF levels as compared to 31% of those with normal SF levels. With increased levels of SF diabetic neuropathy increased. This was found to be significant ($p < 0.05$). 70% of the 50 type-2 diabetic patients with increased SF levels had hypertension as compared to 36% of those with normal SF levels. It was found that those with increased level of SF, more number of patients had hypertension and is found to be significant ($p <0.05$).Out of 50 patients, 29% had increased SF and peripheral vascular disease as compared to 26% of those

Table No.-1 Demographic Characteristic

Characteristics	Cases (N = 50)	Controls (N = 50)
Age	39.10(2.88)	39.00(3.10)
BMI	31.51(1.07)	31.56(1.19)

Table No.-2 Relationship Between SF & SI

Characteristics	SF	SI
Cases (n = 50)	226.70(53.46)	32.06(04.62)
Controls (n = 50)	174(54.90)	31.56(6.827)

Pearson's Product Moment Correlation Coefficient {r= 0.772, p= 0.01, two tallied}

with normal SF levels. There was non significant relationship found between SF and peripheral vascular disease. Out of 50 patients, 32% had ischemic heart disease in those with increased SF and equal percentage of those with normal SF also had ischemic heart disease showing no statistically significant relationship between SF and ischemic heart disease.

Discussion

It was evident from the study that increased body iron stores reflected by SF levels had a statistically significant directly proportional correlation with SI levels. Insulin resistance (IR) is compensated by hyperinsulinemia, which sets in early even before the onset of frank diabetes mellitus and correlate well with SF.

Our findings are in agreement to Wrede *et al* (4) who reported a significant correlation between SF and the presence of insulin resistance criteria in a large representative population. Suvarna *et al* (5) from India reported similar indirect evidence that insulin resistance; sets in early and correlate well with total units of blood transfused and serum ferritin in chronically transfused patients of thalassemia major. Fernandez *et al* (1) found in general population that increased body iron stores are possibly associated with occurrence of glucose intolerance, type-2 diabetes and gestational diabetes. Facchini (8) found significant reduction in serum insulin concentration and improvement in insulin sensitivity after performing phlebotomy. Dymock *et al* (7) reported

Table-3 Relationship Between SF & Various Biochemical Parameters in Diabetic Patients (n=50)

Hb (A1c)	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	22	10	3.36 (C.I.= 0.87-13.16)
SF (Increased)	6	12	1.00
			X^2- Chi Square= 4.09, p=0 .045
TC	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	5	14	1.00
SF (Increased)	21	10	5.88 (C.I.= 1.43-26.10)
			X^2- Chi Square=8.10, p=0.004
TG	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	8	11	1.00
SF (Increased)	24	7	4.71 (C.I.= 1.16-19.58)
			X^2- Chi Square= 6.31, p=0 .01
HDL	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	2	17	1.00
SF (Increased)	15	16	7.97 (C.I.= 1.42-79.61)
			X^2- Chi Square=7.52, p=0.006
UA	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	17	2	1.00
SF (Increased)	13	18	11.729(C.I.=2.05-116.65)
			X^2 –Chi Square=11.09, p=0.0008
LDL	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	4	15	1.00
SF (Increased)	14	17	3.07 (C.I.= 0.73-15.42)
			X^2- Chi Square= 2.97, p=0 .08

Numerical in table are number of subjects with abnormally present or absent biochemical findings. Serum ferritin (SF), serum insulin (SI), total cholesterol (TC), Triglyceride (TG), high density lipoprotein (HDL), uric acid (UA) and low density lipoprotein (LDL).

Table-4 Relationship Between SF & Various Complications in Diabetic Patients (n=50)

Diabetic Nephropathy	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	7	12	1.00
SF (Increased)	25	6	7.14 (C.I.= 1.67-31.75)
			Chi Square X^2 = 9.81, p=0 .001
Diabetic Retinopathy	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	5	14	1.00
SF (Increased)	22	9	6.84 (C.I.= 1.63-30.84)
			Chi Square X^2 = 9.46, p=0 .002
Diabetic Neuropathy	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	6	13	1.00
SF (Increased)	22	9	5.30 (C.I.= 1.32-22.23)
			Chi Square X^2 = 7.42, p=0 .006
Hypertension	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	7	12	1.00
SF (Increased)	22	9	4.19 (C.I.= 1.07-16.84)
			X^2- Chi Square = 5.63, p=0 .01
Peripheral Vascular Disease	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	5	14	1.00
SF (Increased)	9	22	7.97 (C.I.= 0.27-5.29)
			X^2- Chi Square = 0.04, p=0 .83
Ischemic Heart disease	**Present**	**Absent**	**Strength of Association or (95% of C.I.)**
SF (Normal)	6	13	1.00
SF (Increased)	10	21	1.03 (C.I.= 0.26-4.35)
			X^2- Chi Square = 0.02, p=0 .96

Numerical in table are number of subjects with present or absent diabetic complication. Serum ferritin (SF)

significant reduction in total daily insulin dosage following phlebotomy. Similarly Dmochowski *et al* (2) reported in thalassemic patients that serum ferritin concentration correlated negatively with insulin sensitivity. The results of present study are also in agreement with epidemiological studies pointing similar correlation (9, 10).

Jiang *et al* (14) have reported elaboration of hydroxyl radical in iron overload which causes cell damage and leads to insulin resistance. Deferroxamine, a chelating agent with antioxidant properties improve fasting blood glucose in chronically transfused patients of thalassemia major support this hypothesis (5). Recently, it has been suggested that transferrin and iron induce IR of glucose transport in adipocytes (15). However these hypotheses remain to be proved in future.In the patients, we found a positive correlation between increased SF and poor glycemic control reflected by higher HbAIC, supporting the findings of Eschwege *et al* (16).Metabolic syndrome17 include insulin resistance, hypertension, dislipidemia, obesity, type-2 DM and accelerated cardiovascular disease. Iron stores expressed as SF concentration, have been proposed as component of IRS. SF concentration is also directly associated with serum UA another component of the IRS and inversely related with HDL concentration.

In our study a statistically significant correlation was found between body iron stores and hypertension, TC, TG, UA levels and an inverse relationship was found between SF and HDL. These finding, correlate with the fact that phlebotomy is followed by drop in serum glucose, TC, TG and improvement in both beta cell secretion and peripheral insulin action in type-2 DM (8). Findings also correlate with observations made by Wrede *et al* (4) that SF values are significantly increased in patients with high BMI (> 25 kg/m2), increased TC (> 200 mg/dl), increased systolic (> 160 mmHg) blood pressure, DM and in patients with increased diastolic (> 95 mmHg) blood pressure.

The second objectivity of the study was to see the influence of the body iron stores on diabetic complications. DyMock *et al* (7) reported influence of the increase body iron stores on diabetic nephropathy and vascular dysfunction. In patients with increased SF glycemic control is poor and there is vascular damage. Insulin resistance has been documented by Ralpha & Fronzo [18] in such patients. In our study significant correlation was found between increased levels of SF and diabetic nephropathy in accordance to above findings.In a trial by Cantur KZ *et al* (11) poorly controlled patients of diabetes had hyperferritinemia and they found correlation between ferritin level and diabetic retinopathy. The present study

is in accordance to this study.Whereas, persistent hyperglycemia appears to be the primary factor in the pathogenesis of neuropathy, several functional disturbances are found in the microvasculature of the nerves of diabetic patients (19).

These include elements of metabolic syndrome such as insulin resistance, elevated systolic blood pressure and diabetic dyslipidaemics (19). In our study a statistically significant correlation was found between SF and diabetic neuropathy.The evidence from prospective human studies are inconsistent; some patients with increased levels of SF have shown risk coronary heart disease while others have not. Discrepancy may be due to environmental bias and variability in response. Studies by Beyar (20) and Ascherio (6) like our study showed inconsistent effect on coronary heart disease. In our study inconsistent effect of SF levels was found on ischemic heart disease, peripheral vascular disease & LDL levels. In our study only two patients had cerebrovascular disease and in one case SF level was normal and in second case it was increased. So, nothing conclusively could be established about the relationship between SF level and cerebrovascular disease.

Conclusion

It is abundantly clear from the results of present study that increased SF levels are associated with increased SI levels reflecting insulin resistance, poor glycemic control and increased TC, TG and UA except LDL levels in diabetic patients and also associated with complications of type-2 DM like nephropathy, retinopathy, neuropathy and hypertension except peripheral vascular disease and ischemic heart disease.

References

1. Fernandez-Real JM, Lopez-Bermejo A, Ricart. Cross talk between iron metabolism and diabetes. *Diabetes* 2002; 51:2348-54.
2. Dmochowski K, Finegood DT, Francombe W, Tyler B, Zinman B. Factors determining glucose tolerance in patients with thalassemia major. *J Clin Endocrinol Metab* 1993; 77:478-83.
3. Cavallo-Perin P, Pacini G, Cerutti F, Bessone A, Condo C, Sacchetti L, *et al*. Insulin resistance and hyperinsulinemia in homozygous ß-thalassemia. *Metabolism* 1995; 44: 281–86.
4. Wrede CE, Buettner R, Bollheimer LC, Scholmerich J, Palitzsch KD, Hellerbrand C. Association between serum ferritin and the insulin resistance syndrome in a representative population. *Eur J Endocrinol* 2006;154:333-40
5. Suvarna J, Ingle H, Deshmukh CT. Insulin resistance and beta cell function in chronically transfused patients of thalassemia major. *Ind Pediatr* 2006; 43:393-400
6. Ascherio A, Rimm EB. Blood Donation and risk of coronary heart disease in men. *Circulation* 2001; 103: 52-57
7. Dymock IW, Cassar J , Pyke DA, Oakley WG.. Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of haemochromatosis. *Am J Med* 1972; 52:203-10
8. Facchini FS. Effect of phlebotomy on plasma glucose and insulin concentrations. *Diabetes Care* 1998; 21:2190
9. Rajpathak S, Ma J, Manson J, Willett WC, Hu FB. Iron intake and the risk of type 2 diabetes in women: a prospective cohort study. *Diabetes Care* 2006 ; 29:1370-6
10. Jiang R,Ma J, Ascherio A, Stampfer MJ, Willett WC, Hu FB. Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study. *Am J Clin Nutr* 2004;79:70-5
11. Canturk Z, Cetinarslan B, Tarkun I. Serum ferritin levels in poorly- and well-controlled diabetes mellitus. *Endocr Res* 2003; 29: 299-306
12. Loebstein R, Lehotay DC, Luo X, Bartfay W, Tyler B, Sher GD. Diabetic nephropathy in hypertransfused patients with beta-thalassemia. The role of oxidative stress. *Diabetes Care* 1998; 21:1306-9
13. Mascitelli L, Pezzetta F. High iron stores and impaired endothelial function in prediabetic subjects. *Am J Cardiol* 2006; 97:1550
14. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 2004; 291: 711-17.
15. Green A, Basile R, Rumberger JM. Transferrin and iron induce insulin resistance of glucose transport in adipocytes. *Metabolism* 2006; 55:1042-45
16. Eschwege E, Saddi R, Wacjman H, Levy R, Thibult N, Duchateau A. Haemoglobin AIc in patients on venesection therapy for haemochromatosis. *Diabetes Metab* 1982; 8:137-40.
17. Eroglu D, Zeyneloglu HB. Metabolic disorders in patients with recent gestational diabetes mellitus. *J Obstet Gynaecol Res* 2006; 32: 408-15.
18. DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J. Insulin resistance in uremia. *J Clin Invest* 1981 ; 67:563-68.
19. Vinik AI, Erbas T, Stansberry KB, Pittenger GL. Small fiber neuropathy and neurovascular disturbances in diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2001;109 Suppl 2:S451-73.
20. Baer DM, Tekawa IS, Hurley LB. Iron stores are not associated with acute myocardial infarction. *Circulation* 1994; 89: 2915-58