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Total Body Iron Status of a Group of Bangladeshi Prediabetic Subjects

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Summary:

Background: Iron overload has been implicated in the etiopathogenesis of diabetes mellitus, but limitations of the existing markers and involvement of confounding variables have made it difficult to ascertain its precise role in diabetes. Investigation in prediabetic states (Impaired Fasting Glucose or IFG, Impaired Glucose Tolerance or IGT, and combined IFG & IGT or IFG-IGT) may help to clarify the causal relationship between iron overload and diabetes.

Objectives: The present study was undertaken to explore the body iron status in prediabetic subjects. With the above objective a group of nine IFG, twenty four IGT and twelve combined IFG-IGT subjects were studied along with a group of nineteen healthy controls subjects, matched by Age and BMI were included in the study.

Methodology: Serum fasting glucose was measured by glucose-oxidase method and lipid profile was measured by enzymatic-colorimetric method. Insulin secretory capacity (HOMA B %) and insulin sensitivity (HOMA S %) were analyzed by Homeostasis Model Assessment. Serum ferritin was measured by chemiluminescence-based ELISA technique.

Results: Age and BMI were matched among the study subjects. Systolic blood pressure (Mean±SD) among control, IFG, IGT and IFG-IGT subjects were 113±7, 122±22, 123±24 and 122±22 respectively. Systolic blood pressures of IGT subjects were significantly higher (p=0.05) compared to control. Regarding lipid levels, only cholesterol level was significantly higher (p=0.04) in IGT than in controls.

Fasting serum glucose (mmol/l) expressed as median range were significantly higher in IFG (p=0.0001) and IFG-IGT (p=0.0001) compared to the control. Moreover, the IFG subjects showed a significant ß cell dysfunction (p=0.02) as evident from HOMA%B. The insulin sensitivity was significantly (p=0.01) lower in IFG-IGT subjects than in controls as evident from HOMA%S. Fasting serum ferritin (ng/mL) expressed in Median (range) among control, IFG, IGT, and IFG-IGT were 43.9 (7.5-151.0) 51.6 (11.8-158.0), 53.9 (11.3-272.0) and 93.0 (41.8-285) respectively. IFG-IGT subjects (p=0.02) had significantly higher levels of serum ferritin level compared to the controls.

Conclusion: No association was found between serum ferritin and any other biochemical parameters. Serum ferritin did not seem to have a causal role in the pathophysiology of type 2 diabetes and the reported iron overload in diabetic patients seemed to be secondary to other metabolic disorders developed in the disease state.

Key Words: Prediabetes, Impaired Fasting Glucose, Impairede Glucose Tolerance, Ferritin, Insulin resistance, IFG, IGT.

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Introduction:

In recent years there has been considerable interest in the possibility that excessive tissue iron stores may contribute to the pathogenesis of diabetes. Extensive clinical, epidemiological, and basic studies suggest that excessive tissue iron may contribute to impaired glucose tolerance, diabetes mellitus (DM), and the complication of DM[1-2].

Higher serum ferritin concentration has been proposed to be a component of insulin-resistance syndrome. It has been found that serum ferritin measurement was closely correlated with body iron stores in healthy individuals[3].

Several studies had been conducted to explore the relationship of body iron stores with insulin resistance syndrome in type 2 DM. In cross-sectional analysis, it had repeatedly been shown that a third or more of adults

with type 2 DM had elevated serum ferritin[4-5]. Elevated serum ferritin levels independently predicted incidence of type 2 diabetes in prospective studies in apparently healthy men and women[6]. In another study a positive association was found between elevated iron stores measured by serum ferritin level and the prevalence of metabolic syndrome, particularly serum triglyceride and plasma glucose as well as other markers of insulin resistance syndrome[7]. Among 9,486 adults in the United States, about half of men and women with previously unsuspected diabetes (negative history of diabetes but fasting serum glucose e"126mg/dl) had elevated serum ferritin[8]. Further, in adult population serum ferritin had been found to correlate strongly with levels of glucose, insulin, and HbA1c . In a prospective study of 1,038 randomly selected men, those with calculated body iron stores in the highest quartile were found to be 2.4 fold more likely than others to develop diabetes during four years of follow-up[9]. In another study, it was found that serum ferritin could be employed as a marker of not only glucose homeostasis but also insulin resistance in type 2 diabetes[10].

As ferritin can be considered as a risk factor for diabetes type 2, then it should be elevated in prediabetes stages such as subjects with impaired fasting glucose (IFG) who are prone to develop overt hyperglycemia. This study was designed to investigate the association between serum ferritin and IFG, IGT and combined IFG and IGT subjects in Bangladesh.

Materials and Methods:

Forty Five IGT subjects and nineteen controls subjects were collected from the Out-Patient Department (OPD) of the BIRDEM Hospital. The study subjects comprised of the following groups: subjects were considered as IFG or IGT using recently published WHO guidelines (IFG: fasting serum glucose 6.1-6.9 mmol/l and 2h serum glucose <7.8 mmol/l, IGT: fasting serum glucose 6.1-6.9 mmol/l and 2h serum glucose 7.8-11.0 mmol/l).

Nineteen age, sex and BMI matched healthy subjects without family history of diabetes were recruited as controls from the friend circle of the IGT subjects considering as the same socio-economic status. A questionnaire was developed to obtain relevant information of demographic and socio-economic data such as age, educational status, and occupational status.

Results:

A total number of 64 subjects were participated in this study where 09 were isolated IFG, 24 were isolated IGT and 12 were combined IFG-IGT. As a Control group 19 healthy subjects without family history of DM and IGT were recruited.

Table-I

Anthropometric and clinical characteristics of the study subject

Variables	Control (n=19)	IFG (n=09)	IGT (n=24)	IFG+IGT (n=12)	t/p value		
					Control vsIFG	Control vsIGT	Control vsIFG+IGT
Age(Yrs)	38 ± 6	43 ± 6	41 ± 7	43 ± 8	1.61/0.10	1.09/0.28	1.93/0.06
BMI(kg/m^2)	25.4 ± 3.6	25.8 ± 2.9	25.4 ± 4.6	27.7 ± 2.5	0.38/0.70	0.06/0.95	2.17/0.03
WHR	0.93 ± 0.25	0.94 ± 0.04	0.92 ± 0.01	0.92 ± 0.01	1.41/0.17	1.60/0.11	1.12/0.27
Neck (cm)	34.4 ± 3.2	35.2 ± 3.1	33.1 ± 5.5	36.0 ± 3.3	0.65/0.52	0.90/0.36	1.34/0.19
MUAC(mm)	297 ± 21	297 ± 21	301 ± 47	316 ± 33	0.70/0.49	0.84/0.40	2.35/0.03
-Triceps(mm)	15.5 ± 4.5	17.1 ± 4.1	20.3 ± 7.1	21.2 ± 4.8	0.90/0.37	2.65/0.01	3.22/0.004
BFM(%)	29.2 ± 6.2	29.3 ± 7.3	29.7 ± 6.0	29.2 ± 0.5	-.07/3.76	-1.00/1.24	-0.35/2.88
S_BP(mmHg)	113 ± 7	122 ± 22	123 ± 24	122 ± 22	1.7/0.09	2.04/0.05	1.6/0.12
D_BP(mmHg)	75 ± 8	77 ± 11	81 ± 14	79 ± 13	0.7/0.5	1.7/0.10	1.11/0.27

Data were expressed as Mean ± SD. Differences among the groups were calculated using Student 't' test as the test of significance at 5% significance level. n=number of subjects, BMI=Body mass index, WHR=Waist hip ratio, MUAC=Mid upper arm circumference, Sub_S=Subcapular, BFM=Body fat mass, S_BP=Systolic blood pressure, D_BP=Diastolic Blood Pressure.

Age (Mean±SD) among the Control, IFG, IGT and IFG-IGT subjects were 38±6, 43±6, 41±7and 43±8 years respectively. BMI (kg/m^2) was expressed as Mean±SD and the value among control, IFG, IGT and IFG-IGT were 25.4± 3.6, 25.8±4.6, 25.8±2.9, and 27±2.5. respectively BMI was significantly higher in IFG-IGT subjects (p=0.03) compared to control. Fasting serum ferritin (ng/mL) expressed in median (range) among Control, IFG, IGT, and IFG-IGT were 43.9(7.5-151.0) 51.6 (11.8-158.0), 53.9 (11.3-272.0) and 93.0 (41.8-285) respectively. IFG- IGT subjects (p=0.02) have shown significantly higher levels of serum ferritin level compared to control.

Table-II

Biochemical status of the study subjects

Variables	Control (n=19)	IFG (n=09)	IGT (n=24)	IFG-IGT (n=12)	u/p value Control vs IFG	Control vs IGT	Control vs IFG+IGT
F_Glu(mmol/l)	5.2 (4.4-7.1)	6.3 (6.1-6.7)	5.4 (4.3-6.09)	6.2 (6.1-6.9)	-3.7/0.0001	-1.1/0.02	-4.14/0.0001
2h_Glu(mmol/l)	6.2 (3.6-7.4)	6.6 (4.2-7.7)	9.0 (7.8-10.92)	9.7 (8.2-10.73)	-6.4/0.05	-5.57/0.001	-4.6/0.0001
TG(mg/dL)	103.0 (56.0-361.0)	145.0 (67.0-386.0)	144.0 (67.0-254.0)	146.0 (88.0-319.0)	-1.5/0.11	-1.6/0.09	-1.7/0.08
Chol(mg/dl)	171.0 (150.0-261.0)	208.0 (169.0-239.0)	192.5 (145.0-273.0)	189.0 (149.0-269.0)	-2.4/0.13	-2.0/0.04	-1.18/0.24
HDL(mg/dl)	27.0 (21.0-40.0)	37.0 (28.0-57.0)	35.5 (20.0-55.0)	36.00 (24.0-57.0)	-2.9/0.004	-2.8/0.005	-2.5/0.01
LDL(mg/dl)	120.0 (90.8-194.2)	132.0 (100.6-171.0)	123.1 (69.2-218.6)	115.3 (59.4-203.4)	-1.05/0.29	-0.307/0.76	-0.324/0.75
SGPTU/L)	24.0 (12.0-65.0)	10.0 (10.00-16.0)	10.0 (10.0-35.0)	10.0 (10.0-25.10)	-3.9/0.0001	-4.8/0.0001	-3.9/0.0001
S_Crea(mg/dl)	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1.0 (0.9-1.5)	1.0 (0.8-1.3)	-1.3/0.18	-0.80/0.41	-0.69/0.49

Data were expressed as Median (range). Mann-whitney u test was performed as the test of significance 5% significance level. Values in column with different superscripts are significantly different from each other. N=number of subjects. F_Glu-= Fasting glucose; 2h_Glu= 2 hour after glucose; TG= Triglyceride; Chol= Total cholesterol; HDL= High Density Lipoprotein cholesterol; LDL=Low Density Lipoprotein cholesterol; SGPT= Serum glutamate pyruvate transaminase; S_Crea= Serum creatinine

Table-III

Insulinemic and Insulin-Glucose ratio of the study subjects.

Variables	Control (n=19)	IFG (n=09)	IGT (n=24)	IFG-IGT (n=12)	u/p value Control vs IFG	Control vs IGT	Control vs IFG-IGT
F_Ins (µIU/l)	5.0 (1.1-14.8)	8.3 (3.3-12.2)	6.8 (2.1-30.1)	11.8 (3.7-66.00)	-3.8/0 .0001	-1.1/0.27	-4.4/0.0001
Ins:Glu	0.6 (0.3-5.1)	0.7 (0.5-1.8)	0.8 (0.1-1.6)	0.5 (0.1-1.6)	-1.6/0.110	0.66/0.50	-1.2/0.22
HOMA%B	99 (21.0-187.0)	71.6 (39.0-93.0)	77.5 (51.0-264.0)	85.7 (40.0-121.0)	2.5/0.01	-0.94/0.35	-1.05/0.29
HOMA%S	79.6 (44.0-554.0)	74.6 (51.0-185.0)	87.1 (111.0-218.0)	58.9 (34.0-161.0)	-0.117/0.86	-.42/0.68	-2.4/0.015

Data were expressed as Median (range). Mann-whitney u test was performed as the test of significance 5% significance level. Values in column with different superscripts are significantly different from each other. N=number of subjects; F_Ins= Fasting Insulin; HOMA %B= B cell function assessed by homeostasis model assessment; HOMA %S= Insulin sensitivity assessed by homeostasis model assessment; Ins: Glu= Insulin Glucose ratio.

Table-IV

Serum ferritin status of study Subjects

Variables	Control (n=19)	IFG (n=09)	IGT (n=24)	IFG+IGT (n=12)	u/p value		
					Control vs IFG	Control vs IGT	Control vs IFG-IGT
Ferritin(ng/mL)	43.9 (7.5-151.0)	51.6 (11.8-158.0)	53.9 (11.3 - 272.0)	93.0 (41.8 - 285)	-0.271/0.78	-0.6/0.50	-2.3/0.02

Data were expressed as Median (range). Mann-whitney u test was performed as the test of significance 5% significance level. Values in column with different superscripts are significantly different from each other. N=number of subjects.

Discussion:

It is known that iron interferes with insulin inhibition of glucose production by the liver. Hepatic extraction and metabolism of insulin is reduced with increasing iron stores leading to peripheral hyperinsulinemia[11]. The initial and most common abnormality seen in iron overload conditions is liver insulin resistance. Ferritin has long been known as the main site for intracellular storage of excess iron in mammalian tissues.. Liang Sun et al, also found that elevated ferritin concentrations frequently cluster with well-established risk factors of diabetes including obesity, metabolic syndrome, chronic inflammation, and altered circulating adipokines[12].

Although considerable evidence has been generated on the association of serum ferritin with Type 2DM, its causal role in the development of the metabolic disorder has not yet been established and iron overload as a risk factor for diabetes has remained largely speculative[13]. The present study was designed to investigate the association between serum ferritin concentration in IFG, IGT and combined IFG-IGT subjects in a Bangladeshi population.

Forty five IGR (9 IFG, 24 IGT and 12 IFG-IGT) subjects and 19 controls were included in this study. The median serum ferritin level in Bangladeshi control subjects 43.90 ng/l was comparable with the mean value in an Iranian population where they found it as 49.4 ng/l[14]. In our study serum ferritin concentration was not significantly higher in isolated IFG and IGT subjects but it was significantly higher in combined IFG-IGT subjects than the control subjects (p=0.02). This is in contrast with the findings where it was found that ferritin concentration was higher in IFG subjects, compared with normal control subjects[15]. Serum ferritin concentrations were remarkably increased in type 2 diabetes[16].The marginal increase in the IFG-IGT group does in our study not seem to be associated with the diabetic condition as no correlation was found between serum ferritin and any parameter of glycemic (fasting / 2-hour post load glucose) or insulinemic (serum insulin / insulin secretory capacity / insulin sensitivity) status. This finding was also in contrast where a positive association was found between type 2 diabetes and high plasma ferritin concentrations. More recently, a report of 1,013 Finnish men also showed a positive association between ferritin and diabetes[17].

Conclusions:

On overall analysis of the present data it can concluded that serum ferritin does not seem to have a causal role in the pathophysiology of Type 2 diabetes and the reported iron overload in diabetic patients seem to be secondary to other metabolic disorders developed in the disease state.

References:

1. Fernandez- Real JM, Penarroja G, castro A, Garcia-Bragado F, Hernandez Aguado I, Ricart W. Blood letting in High-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function: Diabetes; 2002; 51(4): 1000-1004
2. Salonen JT, Tuomainen TP, Nyyssonen K, Lakka HM, Punnonen K. Relation between iron stores and non- insulin dependent diabetes in men: case –control study: BMJ; 1998; 317:727.
3. Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC(1996) Body size and fat distribution as predictors of stroke among US men: Am J Epidemiol; 1969; 144: 1143-1150.
4. Calballero AE. Endothelial dysfunction, inflammation, and insulin resistance: A focus on subjects at risk for type 2 diabetes: Curr Diab; 2004; 4: 237-246
5. Kissebah A, freedman D, peiris A. Health risk of obesity: Med Clin north Am; 1989; 73: 11-138.
6. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda &

Rizzetto M. Nonalcholic fatty liver, steatohepatitis, and the metabolic syndrome: Hepatology; 2003; 37: 917-923.

7. 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: 711-717

8. Ford ES, Giles WH & Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition examination Survey: JAMA; 2002; 287: 356-359

9. Haap M, Fristsche A, Mensing HJ, Haring HU, Stumvoll M. Association of high serum ferritin concentration with glucose intolerance and insulin in healthy people: Ann Intern Med; 2003; 139(10): 869-871

10. Kim NH, Oh JH, Choi KM, Kim YH, Baik SH, Choi DS, Kim SJ. Serum ferritin in healthy subjects and type 2 diabetic patients: Yonsei Med J; 2000; 41(3):387-92

11. Niederau C, Berger M, Stremmel W, Starke A, Strohmeyer G, Edert R, Siegel E, Creutzfeldt W. Hyperinsulinaemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation: Diabetologia; 1984; 26: 441-444.

12. Liang Sun, Oscar H. Franco, Frank B. Hu, Lu Cai, Zhijie Yu, Huaixing Li, Xingwang Ye, Qibin Qi, Jing Wang, An Pan, Yong Liu, and Xu Lin. Ferritin Concentrations, Metabolic Syndrome, and Type 2 Diabetes in Middle-Aged and Elderly Chinese. J Clin Endocrinol Metab 2008; 93: 4690–4696

13. 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: 711-717

14. Faranak Sharifi, N Mousavi Nasab, H Jazebi Zadeh. Elevated serum ferritin concentrations in prediabetic subjects: Diab Vasc Dis Res; 2008; 5 (1):15-8

15. Sharifi F, Nasab NM, Zadeh HJ. Elevated serum ferritin concentrations in prediabetic subjects: Diab Vasc Dis Res.; 2008; 5(1):15-8

16. Sharif F, Sazandeh SH. Serum ferritin in type 2 diabetes mellitus and its relationship withHbA1c: Acta Medica iranica; 2004; 42(2): 142-145

17. Ren Y, Tian H, Li X, Liang J, Zhao G. Elevated serum ferritin concentrations in a glucose- impaired population and in normal glucose tolerant first-degree relatives in familial type 2 diabetic pedigress: Diabetes Care; 2004; 27(2): 622-623.