Original Article

Serum Ferritin as a Marker of Psychiatric Disorders

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Serum ferritin, insulin resistance (HOMA), lipid profile and Body Mass Index (BMI) were studied on 44 patients of depression and 38 patients of schizophrenia before any specific treatment was initiated, and compared with 30 healthy controls. All studied schizophrenics showed normal BMI and serum ferritin was significantly decreased ($p<0.001$) whereas only about 57% of depressive patients had normal BMI and showed decrease in serum ferritin ($p<0.001$), and rest of the depressive patients had significantly raised BMI ($p<0.001$) as well as raised serum ferritin level ($p<0.001$). Depressive patients with raised ferritin level had significantly raised insulin resistance ($p<0.001$) along with raised serum triglyceride ($p<0.007$). Serum total cholesterol was increased and HDL cholesterol was decreased in both the conditions.

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Key words **: Ferritin, Insulin resistance, Depression, Schizophrenia.**

Depression and schizophrenia are two important psychological disorders in our society. Both the conditions have identifiable biochemical abnormalities of specific neurotransmitters. Nutrition also plays a role in the genesis of these two diseases. It is well established that vitamin B12, folic acid, niacin and vitamin C deficiencies can result in mood disorder[1]. Patients affected by iron deficiency anemia show many mood and behavioral signs and symptoms similar to depressed individual, many of which signs and symptoms appear in the initial stage of iron deficiency (dropped serum ferritin level) before the onset of frank anemia[2].

Data from third National Health and Nutrition Examination Survey (NHNES 3), 1988-1994 indicated that iron deficiency without anemia occurred up to 11% of women (most often pre-menopausal) and 4% of men[3]. Significant decrease in ferritin level in schizophrenic patients has been reported[4]. Alterations in iron metabolism in patients with depression have also been reported in several studies[5-7], whereas Baune B T, *et al* (2006) found no such association[8]. There are reports that depression is frequently linked with insulin resistance[5,9-11] and serum ferritin can be a marker for insulin resistance syndrome[5].

Editor's Comment :

- Psychiatric diseases (Depression & Schizophrenia) may be catagorised in two groups - (a) Low ferritin group. (b) High ferritin group.
- Patients witrh high ferritin group may develop insulin resistance syndrome (Metabolic syndrome) in the long run.
- Serum ferritin may be used as routine parameter for management of those diseases.

The present hospital based case control study was conducted on patients of depression and schizophrenia, compared to control to examine serum ferritin level, insulin resistance (HOMA) and lipid profiles and to find correlation among them in either of these conditions.

Materials and Methods

The present study was carried out during 2008 to 2010 at IPGME&R and BIN, Kolkata in the department of Biochemistry & Department of Psychiatry. Forty four patients of depression and 38 patients of schizophrenia, attending Psychiatric OPD were selected for the study. The patients were selected by criteria given in Diagnostic & Statistical Manual (DSM-4)[12] of mental disorder. The patients were considered for study at their first visit before starting of drug therapy. Thirty healthy individuals without any psychiatric

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disorder were chosen as controls.

Exclusion criteria :

Patients having hemoglobin less than 10gm%, positive CRP, history of taking drugs such as β-blocker, calcium channel blocker and anticonvulsant were excluded. Patients with known diabetes mellitus, coronary heart disease, hematological diseases, liver and thyroid disorders, alcoholism and mal-absorption were also excluded from this study.

Ethical committee of IPGME&R endorsed the study protocol.

Fasting blood samples were collected from the patients and healthy controls. Biochemical parameters, such as fasting plasma glucose, serum insulin, ferritin and lipid profile were done for this study. Serum urea, creatinine, TSH and CRP were done to exclude the conditions under exclusion criteria.

Estimation of Serum Ferritin :

Serum ferritin was estimated by immunoenzymatic sequential assay using ELISA microwells[13].

Estimation of Serum Insulin:

Monobind Insulin Microplate ELISA test was used for the quantitative determination of serum Insulin level[14].

Estimation of Plasma Glucose:

Plasma glucose estimation was done by Glucose Oxidase-Peroxidase method[15].

Estimation of Serum Lipid Profile :

Serum Cholesterol was estimated by Cholesterol Oxidase / PAP method[16]. Serum Triglyceride was estimated by Glycerol Phosphate Oxidase /PAP method[17]. Estimation of HDL cholesterol (Direct) was done by enzymatic method[18].

Estimation of serum urea, creatinine, TSH and CRP (to fulfill the exclusion criteria)

Serum urea and serum creatinine were estimated by Berthelot method and Modified Jaffe's method respectively[19,20]. Serum TSH was estimated by Enzyme Immuno Assay[21]. CRP was estimated by Latex agglutination immunoassay with monoclonal antibody[22].

BMI of the patients were also considered as demographic covariate. It is calculated as follows[23].

$$\mathrm{BMI} = \frac{\mathrm{Weight}\ (Kg)}{[Height(m)]2}$$

Insulin resistance was calculated as HOMA- IR[24].

$$\text{HOMA- IR} = \frac{\text{Fastingplasmaglucose(mg/dl)X FastingInsulin}(\mu IU/ml)}{405}$$

Statistical analyses :

Statistical analyses of data were carried out using SPSS software-version 16. Kruskal Wallis test was employed for comparison of statistical parameters among the groups. Correlation analysis within the groups of depressive patients has been done by Spearman's ranked correlation analysis. Criteria for rejection of null were fixed at the level of 95% confidence.

Results

On analysis it was observed that about 57% of depressive patient showed normal BMI and 43.18% raised BMI in respect to control. We categorized depressive patients into two groups: Group 1 with normal BMI and Group 2 with raised BMI. All schizophrenic patients of this study showed normal BMI in respect to control. Plasma glucose was increased more than control in depression (p value <0.021) and schizophrenia (p value <0.02; Table 1). Basal insulin concentration was increased significantly in Group-2 depression patients (p value < 0.001), but decreased in both Group 1 depression and schizophrenia. In spite of increased basal insulin concentration Group 2 depression patients showed more fasting plasma glucose level than others. So there is a tendency for development of insulin resistance in Group 2 depression as reflected in HOMA-IR value, which was significantly increased in Group 2 depression (p value <0.001). But HOMA-IR value was normal in patients of schizophrenia and Group 1 depression. Serum triglyceride was significantly increased (p value <0.007) in respect to control in Group 2 depression along with fall of HDL cholesterol (p value < 0.005). In this study serum total cholesterol was increased both in depression and schizophrenia in respect to control (p value <0.001 & <0.002 respectively).

Serum ferritin level was significantly decreased in patients of schizophrenia (p value < 0.001), but in case of depression, about 57% of patients (Group 1) showed decreased ferritin whereas 43.18% (Group 2) had increased ferritin level (p value <0.001 & <0.001 respectively) in respect to control (Table 1). In Group 2 depressive patients, serum ferritin level was positively correlated with HOMA-IR (Fig 1; r = 0.98, p<0.001) and also positively correlated with BMI (Fig 2; r = 0.527, p<0.01). Thus irrespective of type of disease, the group of patients having normal BMI showed decreased ferritn with normal insulin resistance and those patients having increased BMI had significantly increased serum ferritin and raised insulin resistance.

Discussion

Vahdat Shariatpanaahi M (2006) reported that there is alteration of iron metabolism in depression. Kuloglu *et al* (2003) observed low iron status in schizophrenic patients. Our observations corroborate these studies in both depression and schizophrenia. According to Sung-Wan Kim *et al*, (2018) study, Iron deficiency may affect dopaminergic transmission in the brain. This iron-dopamine interaction might therefore contribute towards development of symptoms in patients with schizophrenia[25]. Fernandez-Real *et al* (1998) reported serum ferritin to be a marker of insulin resistance syndrome[5]. Ashwan Abdulzahra Hashim (2020) showed in his study that there is a strong relationship between the level of serum ferritin and depression with inverse correlation[26]. One study by Hea Shoon Lee1 and Eunmi Park (2019) provided evidence of existing correlation between ferritin and depression with obesity[27]. In the present study 43.18% of depression cases had raised HOMA-IR and increased BMI (p value <0.001) but the rest of the cases had normal level (Table 1) in respect to control. The depressive patients with raised insulin resistance had also raised ferritin level compared to the other group. Serum ferritin is positively correlated with HOMA-IR (r = 0.98, p value <0.001, Fig 1). The lipid profile was also altered with increased triglyceride and total cholesterol and decreased HDL cholesterol in this group indicating that this group has a tendency to develop metabolic syndrome in future. It is not clear why a part of depressive patients had increased ferritin and insulin resistance and others were free from these changes. Probably this change is related to higher BMI of these patients. Though the sample size was small, this limitation may lead to type 2 error, which might have underestimated the difference from the control population, so the magnitude of the deviation from null is actually more and thus the chance of overestimation of the problem is less. However, the power of the study needs to be increased for better conclusion.

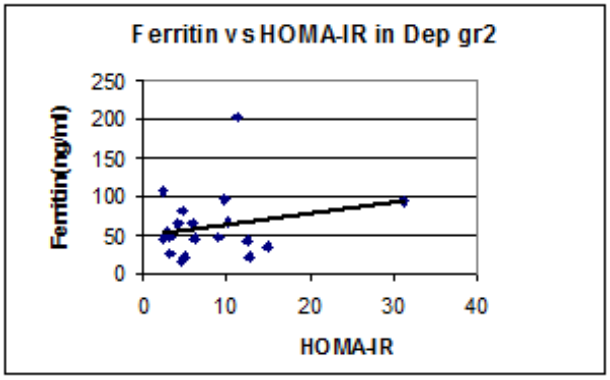

Fig 1 — Correlation of Ferritin and HOMA-IR in Depressive patients (Gr.-2) r = 0.980 (p value <0.001)

Ferritin level was rather decreased than control in schizophrenic cases. No significant changes in HOMA-IR and lipid profile except serum total cholesterol changes in schizophrenic patients was observed in this study indicating that these schizophrenic patients have less chance of developing metabolic syndrome.

It has been observed in previous studies that serum ferritin level is correlated positively with insulin resistance syndrome[9-11]. Our study partially agrees to these findings. Serum ferritin is also correlated with various indices of adiposity[28]. The mechanisms of such an association have not been identified, and it has been hypothesized that the hyperinsulinemia of the metabolic syndrome could be related to an accumulation of iron in the liver[29]. The precise mechanisms underlying the crosstalk between iron

Table 1 — *Biochemical parameters in patients of Group 1 Depression, Group 2 Depression (with Increased BMI in respect to Control) and schizophrenia*

Parameters	Control N =30		Depression (Gr-1) N = 26			Depression (Gr-2) with Increased BMI (N = 18)			Schizophrenia N = 38		
	Mean ± SD	SEM	Mean ± SD	SEM	P value	Mean ± SD	SEM	P value	Mean ± SD	SEM	P value
Plasma Glucose (mg/dl)	84.4±11.7	2.1	92.64±9.69	1.93	< 0.006	120.05±61.12	14.02	< 0.021	93.18±19.9	3.2	<0.02
Serum Insulin (mIU/ml)	7.99±2.17	0.39	4.85±2.91	0.58	< 0.001	26.24±13.47	3.09	< 0.001	5.01±4.2	0.68	<0.001
Serum Ferritin (ng/ml)	66.21±23.91	4.3	36.80±26.66	5.33	< 0.001	96.21±29.92	6.86	< 0.001	31.16±23.14	3.8	<0.001
Serum Triglyceride (mg/dl)	124.9±36.22	6.6	151.72±72.27	14.45	< 0.101	168.53±58.29	13.37	< 0.007	111.63±51.2	8.41	<0.020
Serum total Cholesterol (mg/dl)	143.73±21.8	3.9	186.86±35.96	7.19	< 0.001	197.98±41.23	9.45	< 0.001	171.76±45.7	7.5	<0.002
Serum HDL Cholesterol (mg/dl)	48.86±10.7	1.96	42.09±16.12	3.22	< 0.080	40.31±9.35	2.14	< 0.005	38.75±14.1	2.3	<0.001
HOMA IR	1.69±0.6	0.1	1.09±0.62	0.12	< 0.001	8.08±6.72	1.54	< 0.001	1.21±1.14	0.18	<0.03
BMI (kg/mt^2)	22.38±1.9	0.34	23.02±1.43	0.68	< 0.068	28.93±2.8	0.64	< 0.001	22.91±2.4	0.39	<0.322

stores reflected in hyperferritinemia and the development of insulin resistance remain un-clarified. Elevated ferritin levels may, in concert with other pathogenic factors, play a causal role in the development of impaired beta cell function and decreased insulin sensitivity. Iron mediates oxidative stress[30], and oxidative stress has many deleterious effects[31]. Iron overload has been shown to result in disturbed metabolic activity of the liver as well as skeletal muscle[32] together supporting a role of ferritin in insulin resistance. Increased iron reserve in the liver are postulated to induce liver-mediated insulin resistance with a reduced ability of insulin to suppress hepatic glucose production. Increased iron stores in the liver are postulated to induce liver-mediated insulin resistance with a reduced stability of insulin to suppress hepatic glucose production. Fernandez-Real *et al* (1998) considered that over expression of ferritin probably represents adaptive adiposites response to iron induced oxidative stress resulting in a postiive association between the serum ferritin concentration and the amount of fat tissue in the body[5] as shown by increased BMI in our study. The depression patients, particularly with raised BMI, thus diagnosed by DSM scale should be investigated for serum ferritin level to exclude insulin resistance syndrome. Decreased serum ferritin may also be utilised as a marker of schizophrenia. Ferritin is a major iron storage protein and plays a key role in iron metabolism[33,34]. Serum ferritin concentration provides an indirect estimation of body iron store. Data in men and non-pregnant women had shown that elevated serum ferritin was significantly associated with several cardiovascular disease factors[35]. Positive correlation between mildly increased serum ferritin concentration and indices of insulin resistance in both healthy subject and patient of type-2 diabetes mellitus have been reported[36,37]. Iron plays an important role as cofactor for some enzymes concerned with formation of different

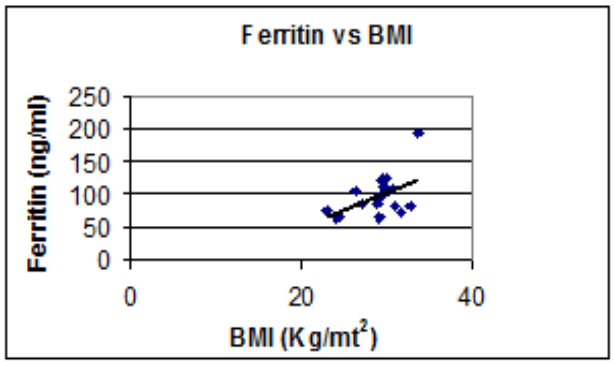

Fig 2 — Correlation of Ferritin and BMI in Depressive patients (Gr.-2) r=0.527 (p value <0.010)

neurotransmitters of brain, some of which are observed to be decreased in schizophrenia. Poor iron status therefore may play a contributing role in the genesis as well as progression of schizophrenia[4].

Despite significant research effort, diagnosis and evaluation of treatment of these psychiatric disorders are still based solely on relatively subjective assessment of symptoms. The search for peripheral markers for psychiatric disorders has been under way for many years but inspite of such efforts a non-invasive blood based test, that can be used for diagnosis and management still remains elusive. Measurement of serum ferritin concentration may be highly useful, non-invasive and cost-effective test for schizophrenia and insulin resistance syndrome in patients diagnosed as cases of depression.

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