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Research Article

PREVALENCE OF METABOLIC SYNDROME AND HYPERHOMOCYSTEINEMIA IN DEPRESSION AND SCHIZOPHRENIA

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ABSTRACT

Depression and schizophrenia are two disabling psychiatric diseases which are complicated by insulin resistance, metabolic syndrome and abnormal homocysteine metabolism. In the present study serum levels of homocysteine and insulin have been measured by ELISA using commercial kits and fasting blood glucose and lipid profile was estimated in Depression (n = 56), Schizophrenia (n = 53) and age and sex matched control subjects (n = 56). The data are compared by ANOVA and post-hoc analysis. The serum homocysteine is markedly elevated compared to control both in Depression and schizophrenia subjects, but to a significantly higher extent in the latter. HOMA-IR is increased in the depressive subjects only compared to control. Likewise, Total cholesterol and LDL cholesterol were significantly higher in both depression and schizophrenia compared to control group. Overall, 38.89% of men and 25% of women have satisfied criteria of metabolic syndrome among depression. On the contrary, prevalence of metabolic syndrome was higher in women (30.77%) compared to men (23.53%) in case of schizophrenia. The analysis of the present data and those published by others suggest that depression and schizophrenia is associated with higher prevalence of metabolic syndrome. Hypertension and dyslipidemia is very common in both groups, but they often remain undetected. This study also indicates that homocysteine metabolism a plays role with respect to depression as well as schizophrenia irrespective of development of metabolic syndrome.

Keywords: Homocysteine, insulin resistance, metabolic syndrome, depression, schizophrenia.

INTRODUCTION

Depression and schizophrenia are two psychological diseases of major public health importance in terms of their prevalence and the suffering, dysfunction, morbidity, and economic burden. People with severe mental illnesses, such as depression or schizophrenia, have a reduced life expectancy compared to the general population [1, 2].They have a 2-3 fold increased risk of dying, and this mortality gap associated with mental illness compared to the general population has widened in recent decades [3]. People with severe mental illness have nearly twice the normal risk of dying from cardiovascular disease [4, 5]. This has led in recent years to a growing concern about physical illness in people with depression or schizophrenia, specifically CVD risk .However, little is understood about mechanisms that may account for poor health outcomes associated with depression or schizophrenia. Previous reports have speculated that depression may be linked to adverse health outcomes through an association with the metabolic syndrome[6]. Despite the body of research implicating depression and the metabolic syndrome as risk factors for CVD, there are few data examining the relationship between depression and the metabolic syndrome.

Similarly, schizophrenic patients are also prone to develop these cardio-metabolic risk factors due to

unhealthy lifestyle, including poor diet and sedentary behavior [7]. But over recent years it has become apparent that antipsychotic agents can have a negative impact on some of the modifiable risk factors [8]. Part of this negative impact can be explained by the liability of some antipsychotics to induce significant weight gain. With an overall increased risk of somatic co morbidities, patients with schizophrenia have poorer access and quality of physical health care.

The lack of epidemiological data in our population regarding the prevalence of metabolic syndrome in depression and schizophrenia subjects prompted us to undertake this study with an objective to compare the prevalence of metabolic syndrome with reference to insulin resistance by HOMA-IR method and ATP III criteria in mental depression and schizophrenia patients with normal control. Furthermore, we have tried to find the association of homocysteine in these two groups of mental illness.

MATERIALS AND METHODS

The study was carried out in the Department of Biochemistry, Medical College, Kolkata and the patients were selected from the Psychiatry Out Patient Department during the period of March 2012 to December 2012. 56 patients of depression and 53 patients of schizophrenia, attending Psychiatric OPD were selected for the study. The patients were selected by criteria given in Diagnostic & Statistical Manual (DSM-4) [9] of mental disorder. 56 age and sex matched control subjects without any evidence of depression or schizophrenia were enrolled into the study as controls. Permission from the Institutional Ethics committee was duly obtained. After fully explaining the study, a written informed consent was obtained from every control subject and patient or a close relative of the latter in case the patient was not in a position to give the consent.

The patients were considered for study at their first visit before starting of drug therapy. Patients having chronic renal failure from any cause especially diabetic and hypertensive nephropathy, patients on haemodialysis, patients on drugs such as methotrexate, phenytoin, theophylline, niacin and fibrates, and hypothyroid patients were excluded from the study.

ATP III Clinical Identification of the Metabolic Syndrome

The metabolic syndrome was identified by the presence of three or more of the following: (1) High blood pressure: ≥130/85 mm Hg or antihypertensive medication use; (2) High triglycerides: ≥150 mg/dL; (3) Low HDL cholesterol: <40 mg/dL in men or <50 mg/dL in women; (4) High fasting glucose: ≥110 mg/dL or antidiabetic medication use; or (5) Abdominal obesity: waist circumference >102 cm in men or >88 cm in women [10].

Biochemical assays

Fasting venous blood samples were obtained from both patients and controls. The sera were stored at -20°C and analysed within 15 days. Serum Hcy assay was done using a commercial kit (Axis, UK) in which both free homocysteine and protein bound homocysteine were enzymatically converted to S-adenosylhomocysteine which was measured by a sandwich ELISA. Serum Insulin was estimated by ELISA (Monobind, Accubind).

Routine biochemical parameters were measured for all the subjects under study using automated clinical analyzer (model Daytona, Randox).

Insulin resistance

Insulin resistance was calculated as homeostatic model assessment estimates for insulin resistance (HOMA-IR) [11]

$$\text{HOMA - IR} = \frac{\text{Fasting plasma glucose (mg/dl) X Fasting Insulin}(\mu IU/ml)}{405}$$

A cut-off HOMA-IR value=4.0 mol µIU/ml (> 95th percentile (HOMA-IR =3.99) was used to define insulin-resistant state.

Statistical analysis

Continuous variables were tested for normality using the Kolmogrov-Smirnov test resulting normally distributed and were expressed as the mean ± standard error of mean of both groups. Comparison of numerical variables between 3 groups – by One-way Analysis of Variance (ANOVA) followed by Tukey's test as post hoc test if ANOVA returns p value < 0.005.

The statistical analyses were performed using Statistica version 6 and SPSS version 17.

RESULTS

The demographic profiles of all the subjects under study were analyzed. Both controls and cases were in the similar age group. When the age groups were analyzed according to sex, no significant difference was observed between the males and the females either in controls or in cases (data not shown).

The results of the present study indicate that waist circumference was found to be increased in both depression and schizophrenia compared to control group (p value <0.001). Both systolic and diastolic blood pressure was significantly increased in depressed patients, but isolated systolic hypertension was observed in schizophrenic subjects compared to control group. Significantly elevated plasma glucose concentration is present in both male as well female subjects suffering from depression, but not in schizophrenia.Patients of depression and schizophrenia did not show any statistically significant alteration in triglyceride level in comparison to control subjects. HDL cholesterol level was significantly decreased in schizophrenic patients compared to control group (p value <0.001), but not in depressive subjects.

From **Table 1,** 38.89% of men and 25% of women have satisfied criteria of metabolic syndrome among depression. On the contrary, prevalence of metabolic syndrome was higher in women (30.77%) compared to men (23.53%) in case of schizophrenia.

HOMA IR, an index of insulin resistance, was elevated in depressed subjects significantly (p value <0.001). Insulin resistance was observed in schizophrenic patients also, though it was not statistically significant compared to control population. **(Fig 1)** 86.6% of depressed and 80.3% of schizophrenic patients had higher total homocysteine values (cut off > 11.9 µmol/L) respectively. Male depressed patients who satisfied criteria for MS showed significantly higher mean value for tHcy (32.23µmol/L) compared to male depressed patients who did not develop metabolic syndrome, **(Fig 2)** but mean tHcy values were not significantly altered in schizophrenic patients with metabolic syndrome compared to patients without metabolic syndrome in case of both male and female study subjects**. (Fig 3)**

DISCUSSION

People with severe mental illness have nearly twice the normal risk of dying from cardiovascular disease [12]. This has led in recent years to a growing concern about physical illness in people with depression or schizophrenia, specifically CVD risk. Previous reports have speculated that depression may be linked to adverse health outcomes through an association with the metabolic syndrome[13]. Despite the body of research implicating depression and the metabolic syndrome as risk factors for CVD, there are few data examining the relationship between depression and the metabolic syndrome. Similarly, schizophrenic patients are also prone to develop these cardio-metabolic risk factors due to unhealthy lifestyle, including poor diet and sedentary behaviour [7].

In our study, 38.89% of men and 25% of women have satisfied criteria of metabolic syndrome among depression. This finding is contradictory to finding of Kindler et al [6]. Their study on patients with unipolar depression found a prevalence of MS to be 50 per cent and associated with female gender.

Björntorp et. al postulated that psychosocial factors, including depression, can activate the HPA axis, producing hypersecretion of corticotrophin-releasing hormone, adrenocorticotropic hormone, and cortisol [14]. This dysregulation of the HPA axis promotes deposition of visceral adipose tissue which secretes inflammatory cytokines such as interleukin (IL)-1 and IL-6 and tumor necrosis factor (TNF) – α [15]. Both IL-6 and TNF- α have been implicated in insulin resistance, which is considered to be the key factor in the metabolic abnormalities of the metabolic syndrome. The proinflammatory response associated with depression may also have a direct effect on dyslipidemia. The prevalence estimates of metabolic syndrome were 26.67% among subjects with schizophrenia. A study by Cohn *et al* from Canada on patients with schizophrenia reported 44.7 per cent prevalence of MS as per ATP III criteria [16]. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) by McEvoy *et al* reported the prevalence of MS as per updated ATP III criteria for schizophrenia at 42.7 per cent [17]. The prevalence of metabolic syndrome was slightly lower in our study subjects compared to others. This observational difference may be due to limited sample population. However, prevalence of metabolic syndrome was higher in women (30.77%) compared to men (23.53%) in our study. This finding is in line with observation of Surendra K. et al [18] that women tend to have a higher prevalence of MS than men.

Depressed patients have significantly higher insulin concentrations compared to control as

well as schizophrenia subjects. HOMA IR, which is an index of insulin resistance, was significantly elevated in them. Similar finding has been observed by Timonen et. al [19]. Insulin resistance could develop as a consequence of an increased release of counter-regulatory hormones associated with depression. However this is contradicted by Lawlor et. al [20]. In their cross sectional study they found that the prevalence of depression decreased linearly with increasing insulin resistance among women without diabetes and then increased among women with diabetes. They proposed that insulin resistance is a determinant of free fatty acids in the blood, which are in turn important in tryptophan metabolism and brain serotonin concentrations. Thus individuals who are insulin resistant may therefore have higher serotonin concentrations and as a result be less likely to be depressed.

78.6% of depressed patients have higher total homocysteine values (cutoff :>11.9 μmol/L) which is much higher than observation by others. Bottiglieri et. al [21] recorded increased plasma tHcy concentrations in 52% of depressed inpatients by using the cutoff: >11.9 μmol/L, whereas Fava et. al [22] observed increased tHcy concentrations in 20%of depressed outpatients (cutoff: > 13.1μmol/L). High concentration of tHcy in depression patients may be connected with a low intake of folate.

86.6% of schizophrenic subjects have higher total homocysteine values (cutoff :>11.9 μmol/L) and mean value was significantly higher (25.13 μmol/L) compared to control subjects (11.92μmol/L). Similar finding has been reported by Neeman et. al [23]. The evidence for an involvement of Hcy in schizophrenia is poor. Besides sporadic case reports, a few studies provided positive results: Regland and colleagues reported to find higher Hcy levels and MTHFR C677T mutation in psychotic subjects more often [24], a finding which was not replicated by another group [25]. Susser et al. restricted a possible relationship between schizophrenia and homocysteinemia to low-folate subjects only [26].

Furthermore homocysteine level was compared in patients having metabolic syndrome with patients who are not having metabolic syndrome in each group to get an idea whether hyperhomocysteinemia is attributable to development of metabolic syndrome.

It is clearly observed that male depressed patients who satisfied criteria for MS showed significantly higher mean value for tHcy (32.23 μmol/L) compared to male depressed patients who did not develop metabolic syndrome.

From our study, it is evident that mean tHcy values were not significantly altered in schizophrenic patients with metabolic syndrome compared to patients without metabolic syndrome in case of both male and female study subjects.

Table 1: Assessment of metabolic syndrome according to ATP III criteria in depression and schizophrenia subjects

	Depression		Schizophrenia	
	Men (n=18)	**Women (n=12)**	**Men (n=17)**	**Women (n=13)**
Increased waist circumference • Men (>102 cm) • Women (>88 cm)	27.7%	58.3%	5.8%	38.4%
High TG (≥150 mg/dl)	66.6%	25%	35.2%	30.7%
Low HDL • Men (<40 mg/dl) • Women (<50 mg/dl)	55.5%	41.6%	58.8%	61.5%
High fasting glucose (≥110 mg/dl)	38.8%	33.3%	23.5%	15.3%
High BP (≥ 130/85 mm Hg)	44.4%	16.6%	23.5%	38.4%
Metabolic syndrome present (presence of three or more of the components described above)	**38.8%**	**25%**	**23.5%**	**30.7%**

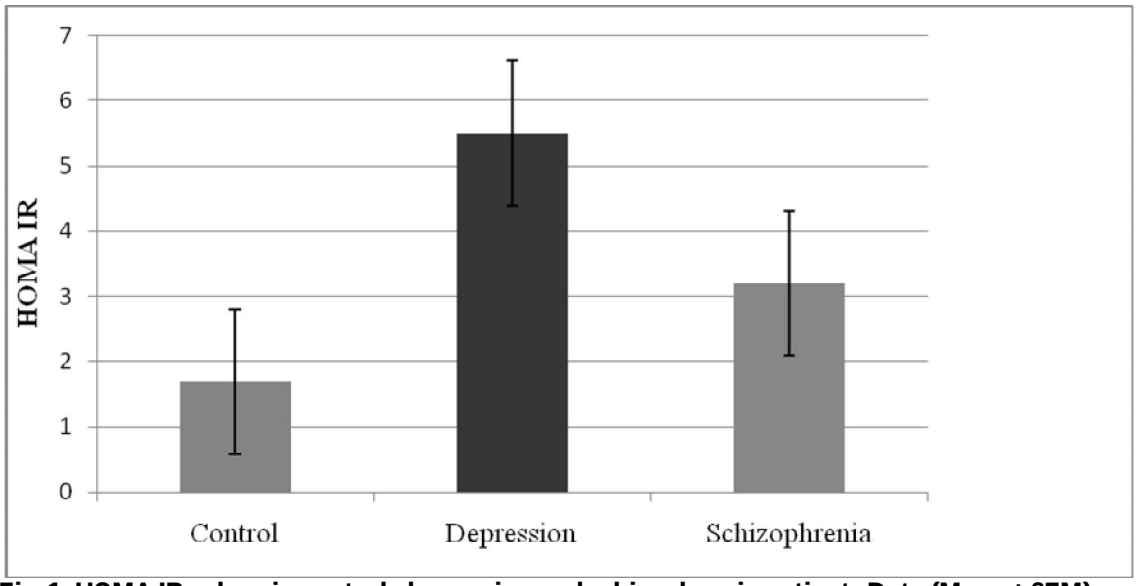

Fig. 1: HOMA IR values in control, depression and schizophrenia patients Data (Mean ± SEM) are expressed. Statistically significant difference (p value < 0.05) is observed between control and depression group

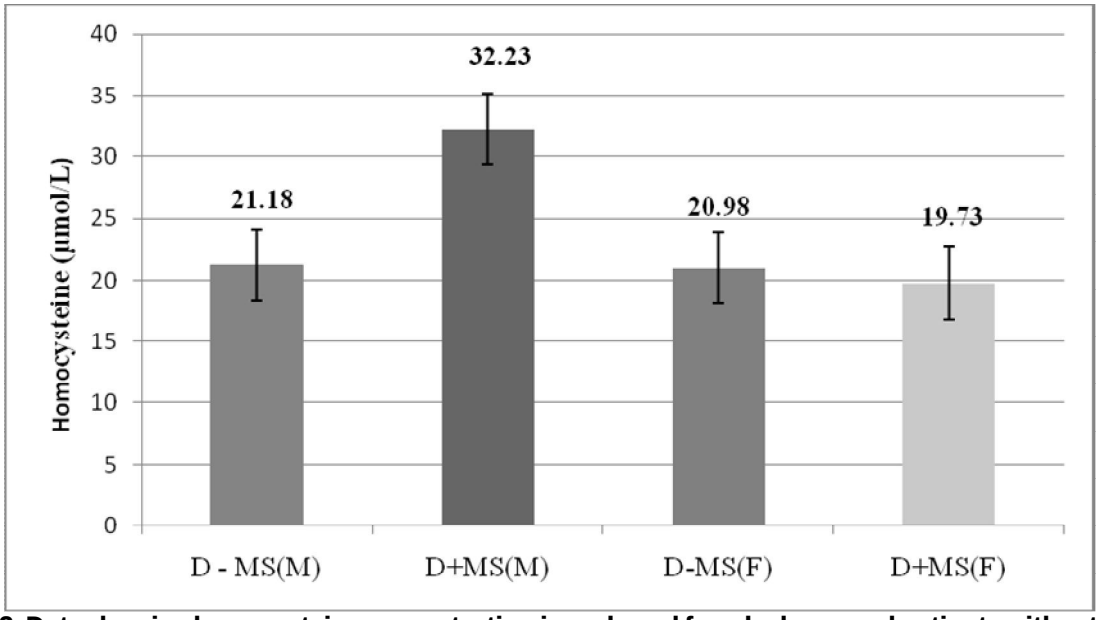

Fig. 2: Data showing homocysteine concentration in male and female depressed patients without and with presence of metabolic syndrome .D-MS (M) - Male depressed patients who did not have metabolic syndrome, D+MS (M) - Male depressed patients who have metabolic syndrome, D-MS (F) - Female depressed patients who did not have metabolic syndrome, D+MS (F) - Female depressed patients who have metabolic syndrome. Data (Mean ± SEM) are expressed as µmol/L of homocysteine concentration. No significant difference was observed

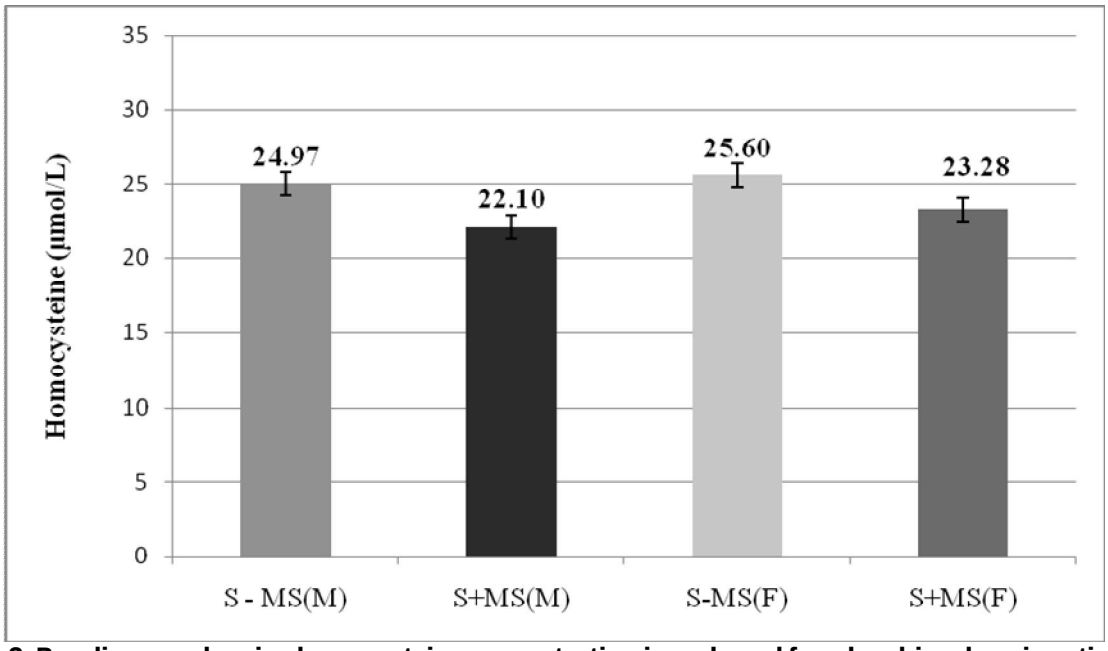

Fig. 3: Bar diagram showing homocysteine concentration in male and female schizophrenic patients without and with presence of metabolic syndrome .S-MS (M) - Male schizophrenic patients who did not have metabolic syndrome, S+MS (M) - Male schizophrenic patients who have metabolic syndrome, S-MS (F) - Female schizophrenic patients who did not have metabolic syndrome, S+MS (F) - Female schizophrenic patients who have metabolic syndrome. Data (Mean ± SEM) are expressed as µmol/L of homocysteine concentration. No significant difference was observed

CONCLUSION

This study indicates that homocysteine metabolism plays a role with respect to depression as well as schizophrenia irrespective of development of metabolic syndrome.

Homocysteine levels in plasma are influenced by various factors such as genetic, dietary and lifestyle factors which can interfere with transsulfuration and remethylation or by pre-existing diseases associated with homocysteine metabolism. The possibility of unadjusted confounding makes it difficult to be sure that the relation between schizophrenia or depression and homocysteine is causal. Vitamin B12 and folic acid status, which could adversely affect homocysteine level, could not be estimated.

Lowering of elevated homocysteine in these groups with folate or B12 supplementation seems sensible, especially as it is inexpensive and has no adverse effect.

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