Assessment of Insulin Resistance and Metabolic Syndrome in Drug Naïve Patients of Bipolar Disorder

Prathama Guha · Kaushik Bhowmick ·
Piyanku Mazumder · Malay Ghosal ·
Indranil Chakraborty · Prabir Burman

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Abstract The levels of fasting glucose, fasting insulin, insulin resistance (IR) and the prevalence of metabolic syndrome (MS) in a sample population of bipolar disorder (BPD) patients who were newly diagnosed and psychotropically naïve were assessed and compared with an age, sex and racially matched control population. 55 BPD-I patients (15–65 years) who were non-diabetic, nonpregnant, and drug naïve for a period of at least 6 months were included in the study. Diagnosis was made using the structured clinical interview for DSM-IV axis I disorders (SCID IV). IR was assessed using homeostasis model of insulin resistance (HOMA-IR); MS was defined according to National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III). Data were compared with 25 healthy

controls. BPD patients had significantly higher mean levels of fasting plasma insulin (13.2 ± 9.2 vs. 4.68 ± 3.1 μ IU/ml, $p < 0.05$), postprandial plasma insulin (27.2 ± 14.5 vs. 18.1 ± 9.3 μ IU/ml, $p < 0.05$) and a higher value of HOMA-IR (3.16 ± 2.2 vs. 1.19 ± 0.8 , $p < 0.05$) when compared to the controls. A significantly higher proportion of patients of BPD compared to controls were manifesting levels of fasting plasma glucose, serum triglyceride and blood pressure higher than the cut off while waist circumference and serum HDL cholesterol failed to show any significant difference in the proportion. There was a significantly higher proportion of prevalence of IR between BPD cases and controls (26/55 vs. 2/25, z value 9.97, $p < 0.05$) while there was no significant difference in proportion of prevalence of MS between these two groups. Within BPD patients, logistic regression analysis showed that age, sex or current mood status (depressed/manic) were not significantly predictive of presence or absence of MS or increased IR.

P. Guha · M. Ghosal
Department of Psychiatry, Medical College & Hospital, Kolkata,
West Bengal, India

K. Bhowmick (✉)
BC-39/6, Deshbandhu Nagar, Baguiati, Kolkata 700059,
West Bengal, India
e-mail: drkbhowmick@gmail.com

K. Bhowmick
Department of Biochemistry, Malda Medical College &
Hospital, Kolkata, West Bengal, India

P. Mazumder
Department of Biochemistry, Medical College & Hospital,
Kolkata, West Bengal, India

I. Chakraborty
Department of Biochemistry, Malda Medical College &
Hospital, Malda, West Bengal, India

P. Burman
Department of Statistics, University of California Davis, Davis,
CA, USA

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Introduction

Obesity and cardiovascular disease, both of which are associated with resistance to insulin action, are known to be common in bipolar disorder (BPD). Epidemiological studies have indicated increased metabolic disturbances, viz metabolic syndrome (MS), hyperinsulinemia and abnormal insulin resistance (IR) in medicated BPD patients, both in the west and in Asian populations, including India [1]. However, metabolic dysfunction has been reported in patients with BPD even before the initiation of psychotropic medications. This implies that intrinsic neuroendocrine

features of BPD may lead to somatic metabolic dysfunctions. Existing evidence suggests that both the disease itself and the prescribed medications may be associated with metabolic disturbances in BPD patients. One of the earliest indicators of subsequent development of MS is impaired insulin responsiveness, as measured by IR. An increased IR is presumed to be central to the development of the MS and may provide the initial, underlying process from which other abnormalities evolve [2].

However, to our knowledge, very few studies, especially in the Indian subcontinent with its unique dietary habits, behavioral patterns and socioeconomic conditions, have been attempted to specifically assess the level of IR and metabolic abnormalities in bipolar patients. This particular field requires further exploration not only for understanding the basis of any pathophysiological process which unites these apparently unrelated disorders, but more so due to the fact that IR and metabolic disorders including diabetes mellitus (DM) have been increasing steadily in the Indian society.

In this context, the present study was planned as a primary baseline study with the aim of examining the relationship between the level of IR and MS in a sample of 55 patients of BPD and comparing it with that in a control group comprising of 25 otherwise healthy, race, age and sex-matched individuals. The objectives of the study were to compare the various participant characteristics including metabolic parameters for diagnosis of MS and IR between newly diagnosed BPD patients and age and sex-matched healthy controls. Secondly, the proportion of patients with MS and significant IR was evaluated in these two group of subjects in order to ascertain whether any statistically significant deviation existed between them. The authors hypothesized that the patients of BPD would have a significantly higher level of IR and greater abnormalities in the metabolism of carbohydrates and lipids compared to the control population. They further hypothesized that a higher proportion of these patients would have MS. The findings of the study may be interesting in the sub-continent, where the population has widely divergent dietary habits, lifestyle and behavioral patterns and socioeconomic conditions compared to their western counterparts. Further, it was presumed that the observations may have clinical relevance in that the patients and their providers should be able to recognize the importance of the relationship between bipolar symptoms and the risk factors for the development of diabetes, hypertension, CAD, which would undoubtedly be of immense benefit in preventing or reducing morbidity and mortality in those suffering from BPD.

Materials and Methods

The study was conducted by the Department of Psychiatry, Medical College and Hospital Kolkata, in collaboration with the Department of Biochemistry, Medical College and Hospital Kolkata. After obtaining ethical clearance from the institutional ethical clearance committee, subjects were selected randomly from BPD patients attending the Psychiatry Outpatient Department who were not on any psychotropic medication for a period of last 6 months or more. The diagnosis of BPD I was confirmed by two psychiatrists in accordance with DSM-IV TR criteria using the structured clinical interview for DSM-IV axis I disorders. (SCID I) [3].

The authors included BPD I patients who were 15–65 years of age, non-diabetic, non-pregnant, and were drug naïve for a period of at least 6 months. All patients with a history of diabetes, substance abuse in last 6 months or any other psychiatric comorbidity and a history of intake of glucocorticoids, hormone replacement therapy (HRT) or Oral Contraceptives (for women) within last 6 months were not eligible and thus were excluded from the study population.

Controls were defined as race, age and sex-matched otherwise healthy individuals who had no lifetime history of any psychiatric disorder and have never received any psychiatric medications. 55 cases of BPD, comprising of 25 males and 30 females were selected randomly. 25 controls, comprising of 12 males and 13 females satisfying the criteria were finally included in the study. Informed consent was obtained from all the participants of the study using Indian Council of Medical Research (ICMR) proforma [4]. A detailed semi-structured proforma was used to record sociodemographic variables, dietary history, working habits, family history, past and present medical history and drug history. A thorough physical examination was performed including blood pressure, height, body weight, waist and hip circumference for all the cases and controls.

IR was calculated by the homeostasis model of insulin resistance (HOMA-IR) [5]. HOMA-IR is considered a surrogate index of IR suitable for use in epidemiological studies in which more invasive measures of IR are prohibitive [6]. Greater HOMA-IR values indicate reduced insulin sensitivity or higher IR. Glucose and insulin were measured from blood specimens obtained after a 12-h fast. IR was calculated as [7]:

Other assay parameters including those for serum cholesterol, serum triglyceride, serum creatinine and plasma

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

glucose 2 h after ingestion of 75 g of glucose were estimated under standardized conditions utilizing commercially available assay kits. Plasma glucose was measured by enzymatic utilising glucose oxidase–peroxidase method of Trinder [8]. Serum creatinine was assayed by its reaction with alkaline picrate, as described by Jaffe [9]. Serum cholesterol was measured by enzymatic method utilising cholesterol oxidase–peroxidase [10]. Serum triglyceride was measured by enzymatic method utilising lipase, glycerokinase, glycerophosphate oxidase and peroxidase as described by Bucolo and David [11]. The diagnosis of MS was performed as per the definition of National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) [12]. The data obtained was statistically analyzed.

Results

Table 1 shows the mean and standard deviation (SD) of baseline participant characteristics in BPD subjects and controls. It was observed by unpaired ‘*t*’ test for calculation of the significance of difference in means between cases and controls that there was no significant difference in individual parameters between the two groups except in the levels of fasting and postprandial plasma insulin and HOMA-IR [13].

Table 1 Participant characteristics

Parameter (unit)	Cases M ± SD	Controls M ± SD	<i>p</i> Value
Age (years)	43.2 ± 10.6	44.7 ± 9.8	>0.05
Height (cm)	151 ± 23.7	157 ± 19.3	>0.05
Waist circumference (cm)	88 ± 11.2	93 ± 10.4	>0.05
Weight (kg)	61.8 ± 20.9	56.1 ± 13.7	>0.05
Blood pressure systolic/ diastolic (mmHg)	119 ± 31/ 78 ± 18	107 ± 34/ 71 ± 23	>0.05
Fasting plasma glucose (mg/dl)	94.6 ± 18.9	89.7 ± 17.2	>0.05
Fasting plasma insulin (μIU/ml)	13.2 ± 9.2	4.68 ± 3.1	<0.05*
Postprandial plasma glucose (mg/dl)	122.3 ± 45.1	122.3 ± 48.9	>0.05
Postprandial plasma insulin (μIU/ml)	27.2 ± 14.5	18.1 ± 9.3	<0.05*
Serum total cholesterol (mg/dl)	163.0 ± 41.9	185.9 ± 37.9	>0.05
Serum HDL cholesterol (mg/dl)	42.6 ± 3.1	43.6 ± 4.4	>0.05
Serum triglyceride (mg/dl)	41.3 ± 66.4	135.68 ± 57.5	>0.05
Serum creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	>0.05
HOMA-IR	3.16 ± 2.2	1.19 ± 0.8	<0.05*

* Significant at 5 % level

BPD patients had significantly greater mean levels of fasting plasma insulin (13.2 ± 9.2 vs. 4.68 ± 3.1 , $p < 0.05$), postprandial plasma insulin (27.2 ± 14.5 vs. 18.1 ± 9.3 , $p < 0.05$) and a higher value of HOMA-IR (3.16 ± 2.2 vs. 1.19 ± 0.8 , $p < 0.05$) as compared to the controls.

Table 2 shows the number and percentage of subjects with value of individual parameters above the cut off for MS as per the criteria defined by NCEP-ATP III. The significant error of difference between two proportions was calculated by normal deviate *z* test [14]. It was observed that a significantly higher proportion of patients of BPD, as compared to the controls, were manifesting levels of fasting plasma glucose (22/55 vs. 5/25), serum triglyceride (23/55 vs. 4/25) and blood pressure (7/55 vs. 2/25) higher than the cut off, while waist circumference (9/55 vs. 5/25) and serum HDL cholesterol (25/55 vs. 15/25) failed to show any significant difference in the proportions.

Table 3 shows the proportion of all subjects with MS and significant IR, further segregated to show the proportion of BPD cases and controls with significant MS. It was observed utilising normal deviate *z* test that there was a significantly higher proportion of IR between BPD cases and controls (26/55 vs. 2/25, *z* value 9.97, $p < 0.05$) while there was no significant difference in proportion of subjects with MS between these two groups [14].

Within BPD patients, logistic regression analysis showed that age, sex or waist circumference were not significantly predictive of HOMA-IR (Table 4).

Table 2 Number (*n*) and percentage (%) of subjects with value of parameters above cut-off for metabolic syndrome* and significance of difference in proportion between cases and controls groups

Parameter	All <i>n</i> = 80	Cases <i>n</i> = 55	Controls <i>n</i> = 25	<i>p</i> Value
Waist (>102 cm)	14 (18 %)	9 (16 %)	5 (20 %)	>0.05
Blood pressure (≥130/ ≥85 mmHg)	9 (11 %)	7 (13 %)	2 (8 %)	<0.05**
Serum HDL cholesterol (men: <40 mg/dl, women: <50 mg/dl)	40 (50 %)	25 (45 %)	15 (60 %)	>0.05
Serum triglyceride (≥150 mg/dl)	27 (34 %)	23 (42 %)	4 (16 %)	<0.05**
Fasting plasma glucose (≥100 mg/dl)	27 (34 %)	22 (40 %)	5 (20 %)	<0.05**

* Metabolic syndrome definition as per criteria of National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III)

** Difference in proportion between cases and controls significant at 5 % level

Table 3 Prevalence of metabolic syndrome (MS) and significant insulin resistance (IR)

Parameter	All <i>n</i> = 80	Cases <i>n</i> = 55	Controls <i>n</i> = 25	<i>z</i> Value	<i>p</i> Value
Metabolic syndrome*	7	5	2	0.43	>0.05
Significant insulin resistance**	28	26	2	9.97	<0.05***

* Metabolic syndrome definition as per criteria of National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III)

** Significant insulin resistance defined as absolute value of insulin resistance (HOMA-IR) ≥ 2.5 [7]

*** Difference in proportion between cases and controls significant at 5 % level

Table 4 Logistic regression analysis for HOMA-IR*

Predictor	Coef	SE Coef	<i>T</i>	<i>p</i> Value
Constant	0.2466	0.5245	0.47	0.640
Age	−0.002925	0.005732	−0.51	0.611
Sex	−0.0413	0.1448	−0.29	0.776
Waist circumference	0.009236	0.006069	1.52	0.132

* Regression equation: HOMA IR = 0.247 − 0.00293 age − 0.041 sex + 0.00924 waist circumference (cm) + 0.669 group

Discussion

One of the interesting aspects of this study was that the patients of BPD were psychotropically naive in whom the confounding effect of psychotropic medication had been effectively eliminated. Yet, the observation of significantly raised fasting insulin, post-prandial insulin and HOMA-IR levels in them compared to controls may help to justifiably bring us to the question of why patients of BPD were inherently vulnerable to metabolic abnormalities. Several mechanisms by which the adverse mental state in BPD may contribute to development of subsequent IR and possibly Type 2 DM have been suggested. In particular, excess cortisol, central adiposity, altered immune function and behavioral factors such as low adherence and physical activity have been observed to play vital roles in the development of MS.

In both the depressive and manic phases of BPD, there is a positive association between chronic stress and elevated cortisol [15]. Elevated glucocorticoids from hypothalamic–pituitary axis (HPA) hyperactivation impedes glucose uptake by insulin, which in turn promotes metabolic dysfunction. Dysregulation of the HPA axis is also associated with elevated levels of leptin. Abnormalities in leptin signaling can lead to obesity and abnormal insulin sensitivity. Another consequence of elevated cortisol is increased

activity of lipoprotein lipase, which increases the amount of adipose tissue [16]. Elevated cortisol secretion also causes IR in muscles and affects the function of glycogen synthase, which then leads to peripheral IR. Mechanisms by which depression may contribute to IR and altered glucose metabolism have been suggested by various workers. It has been postulated that major depressive disorders alter the hypothalamic–pituitary–adrenal axis and can lead to excess cortisol secretion [17]. This may, in turn contribute to visceral fat deposition and increase IR [18]. In fact, it has been documented that acute mood symptoms may be preceded and accompanied by increases in adrenocorticotrophic hormone levels [19]. The disturbances in cortisol regulation seen in BPD play a role in the development of core manifestations of MS, such as IR, hyperglycemia, obesity and dyslipidemia.

That the development of DM and BPD share alterations in several points including that at the level of signal transduction has been suggested [20]. For example, disturbances in glycogen synthase kinase 3 β (GSK 3 β) signaling has been documented to play a role in IR—one of the processes involved in the etiology of Type 2 DM. GSK 3 β is also one of the targets for lithium action. It has been interesting to note that lithium has been shown to possess insulin-like effects in human, animal and in vitro studies [21, 22]. It has also been proposed that disturbances in glucose metabolism or predisposition to DM may contribute to manifestation of psychiatric illness in genetically predisposed individuals. However, to date there are not enough data to allow a definitive conclusion.

In the present study, it was observed that BPD was significantly related to a higher mean level of fasting insulin and a higher level of IR, as indexed by HOMA-IR. However, there was no significant elevation in fasting glucose, post prandial glucose, cholesterol and prevalence of MS in the bipolar group. This corroborated in part to the authors' hypothesis that the patient of BPD would have a significantly higher level of IR and were consistent with previous studies [23, 24].

While conceptualizing this study, the authors had hypothesized that the patients of BPD would have significantly greater abnormalities in the metabolism of carbohydrates and lipids compared to the control population and that a higher proportion of these patients would have MS. The diagnosis of MS was performed as per the definition of NCEP-ATP III [12]. Under this definition, a waist circumference of more than 40" (>102 cm) in men and more than 35" (>88 cm) in females is used to determine central obesity, which is a marker for more atherogenic intra-abdominal or visceral obesity. Conversely, the WHO definition uses body mass index (BMI) to estimate intra-abdominal obesity; this measure does not reliably reflect visceral adipose tissue in various populations, including most Asians [25]. This distinction is important because studies have

demonstrated a higher concentration of adipose-related, deleterious free fatty acids (FFAs) en route to the liver by way of the splanchnic circulation in patients with demonstrated increased visceral fat relative to those with higher subcutaneous fat [26]. Thus waist circumference in preference to BMI had been used as a parameter for diagnosis of MS.

It was observed that in spite of an apparent increase in proportion of MS observed in BPD cases, there was no significant difference in this proportion between BPD patients and the control population. This finding was also in contrast to observations of other workers who have reported a significant increase in the prevalence of MS in BPD patients. The increased prevalence of obesity in BPD patients reported in most western studies is possibly related to the dietary habits of these patients who consume more sugar and carbohydrates than controls [27, 28]. The absence of an increased prevalence of MS in BPD in our study is likely to be due to lifestyle differences in the Western versus the Indian population but, to our knowledge, no study has specifically handled this issue [29]. There are studies, however, that have pointed out that some Asian population are differentially affected by IR and DM [21]. Another reason for the absence of MS could be that we were examining psychotropically naive subjects.

One of the most robust findings of the present study was increased IR in the BPD group. Impaired insulin responsiveness is presumed to be central to the development of the MS and may provide the initial, underlying process from which other abnormalities evolve [2]. The study results suggest that though the newly diagnosed drug naive patients with BPD did not manifest a higher proportion of MS among them, they were at potential risk to develop metabolic abnormalities including MS in future, as revealed by their increased IR. The patients also suffered from significantly higher levels of fasting plasma insulin level. Hyperinsulinemia, a surrogate for IR and a marker for MS, is, in itself, associated with a two to threefold increase in cardiovascular disease independent of classical risk factors.

A search of relevant literature revealed that the study of the influence of gender on MS and/or its components have not received adequate attention in BPD research. Yumru et al. [30] have analyzed the influence of gender on MS (but not its components), failing to find a statistically significant association. However, Mattoo and Singh [31] found a trend of female preponderance for the prevalence of MS across different diagnoses among psychiatric inpatients. In the present study, logistic regression analysis showed that sex was not significantly predictive of HOMA-IR in BPD cases.

The current study however suffers from certain limitations. First, and most importantly, the current sample of patients with BPD was relatively small. Furthermore, it consisted mainly of patients who were newly diagnosed and not receiving any psychiatric medications, and may

thus not be representative for bipolar patients in general. Second, it is a cross-sectional study. This means that the observed associations should be viewed as such and not necessarily interpreted as causal relations. The authors intend to follow up this cohort prospectively, in order to assess metabolic changes during the course of the illness and the function of antipsychotic regimes. Third, other parameters, such as dietary habits, physical activity level and psychopathological profile were not included in the study. Fourth, patient recruitment was restricted to one site, which could have influenced our results, since large regional differences in the prevalence of metabolic abnormalities have been reported. Future research should address these issues more specifically, in large, multi-site samples and with prospective study designs.

In conclusion, our data confirm significantly increased IR among newly diagnosed, drug naïve BPD cases in comparison to control population. However, it was observed that in spite of an apparent increase in proportion of MS observed in BPD cases, there was no significant difference in this proportion between BPD patients and the control population. The current results suggest that though the newly diagnosed patients with BPD did not manifest a higher proportion of MS among them, they were at potential risk of developing metabolic abnormalities including MS in future perhaps arising from increased IR. The hazard posed by the occurrence of MS in BPD cases necessitates the need for practitioners and care givers to carefully screen all BPD patients for risk factors related to metabolic abnormalities as well as careful clinical surveillance for incident disturbances in any metabolic parameter. The selection and sequencing of psychotropic agents in managing BPD need to be informed by possible metabolic disruption. The incorporation of psychosocial treatment strategies that emphasize educational aspects related to metabolic risk and metabolic comorbidity hold promise to reduce the burden of illness and improves outcome in BPD. A second phase study based on the observations of this primary baseline study has been planned in order to investigate a plausible 'cause-effect' relationship between development of MS and IR with BPD. This later finding may serve to plan effective management protocols in future for considerably reducing the morbidity and mortality and economic burden on the society.

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