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Original Research Article

EVALUATION OF THE LIPID AND THYROID PROFILES OF PATIENTS WITH BIPOLAR DISORDER HAVING DIABETES MELLITUS: A TERTIARY HOSPITAL BASED STUDY

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Abstract

Background: Bipolar disorder (BD) is a very debilitating psychiatric disease that affects around 2% of the general population during their lifespan. Individuals with bipolar disorder (BD) may have medical comorbidities, such as metabolic syndrome (MetS), which is characterised by abnormal blood levels of glucose, cholesterol, and triglycerides. These comorbidities can be attributed to various risk factors, etiological processes, and the long-term use of psychotropic drugs. Furthermore, there may be a correlation between the lipid content and the intensity of mental symptoms. **Aim:** To assess the lipid and thyroid profile of bipolar disorder patients with comorbid Diabetes Mellitus. **Materials & Methods:** A cross-sectional research was conducted at the Department of Psychiatry from December 2011 to May 2012. A total of 50 consecutive individuals diagnosed with Bipolar Affective Disorder, according to the D.S.M.-IV-T.R. criteria, and aged between 18 and 65 years, were included in the research after providing written informed permission. A distinct clinical proforma was used to document the clinical associations, socio-demographic information, physical examination observations, and laboratory investigation results. The blood samples underwent the following laboratory investigations: Tests were conducted to measure the levels of fasting blood sugar, post prandial blood sugar, glycosylated haemoglobin, fasting lipid, and thyroid profile. **Results:** 26% of the patients had Cholesterol levels above 200mg/dl whereas 74% had it in the normal range. 20% of patients had elevated L.D.L. levels and 80% had it in the normal range. 58% of patients had H.D.L. levels below 40mg/dl while 42% had above. 92% of patients had T3 levels in the normal range and 88% had T4 levels in the normal range. 4% of patients had elevated T3 and T4 and 4% and 8% of patients respectively had T3 and T4 levels below normal range 86% of patients had T.S.H. levels in the normal range. 10% of patients had elevated T.S.H. (>6.2) and 4% had lower levels of T.S.H. **Conclusion:** We concluded that 26% of the patients had Cholesterol levels above 200mg/dl, 20% of patients had elevated L.D.L. levels and 58% of patients had H.D.L. levels below 40mg/dl. With reference to the thyroid status of the bipolar sample, it was found that only 8% of patients had abnormalities in T3 levels, 12% in T4 levels and 14% of patients had abnormal T.S.H. levels.

INTRODUCTION

Bipolar disorder (BD) is a collection of affective illnesses distinguished by the occurrence of repeated manic or hypomanic episodes that may alternate with significant depression periods.[1] Recent epidemiological studies have shown that the expected lifetime prevalence of BD is around 2.4%.[2] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) incorporates the classification "Bipolar and related disorders", which contains Bipolar Disorder type I, Bipolar Disorder type II, and cyclothymic disorder. The category of "other specified and bipolar-related disorders" include unusual bipolar-like occurrences that do not conform to the conventional categories. BD is ranked as the 17th most common cause of disability globally, considering its characteristics and widespread

occurrence.[4] Furthermore, it is linked to elevated levels of premature death caused by both medical comorbidities and a high incidence of suicide.[1] Psychopharmacological therapies are followed by a significant number of individuals with BD throughout their lives. International recommendations encourage the use of medications such as mood stabilisers, oral and long-acting antipsychotics, and antidepressants for both the treatment of acute mood episodes and the prevention of relapses. These medications are used both on-label and off-label.[5,6] Nevertheless, psychiatric drugs are not devoid of side effects, which might include hepatic malfunctions, renal, thyroid, and parathyroid dysfunctions, as well as metabolic syndrome (MetS).[7-10]

The metabolic syndrome is a compilation of established individual risk factors for coronary artery disease (CAD) with the potential to dramatically increase the incidence of heart disease and diabetes mellitus, and all-cause mortality. Hypertension, dyslipidemia, glucose dysregulation, and obesity are the core components of the metabolic syndrome. The assemblage of metabolic disturbances as a distinct entity was described over 90 years ago by Kylin in 1923 when he found that hyperglycaemia, gout, and hypertension were correlated with negative cardiovascular outcomes. In 1988, Reaven proposed the term "syndrome X" to identify the CAD risk factors of dyslipidaemia, hyperglycaemia, and hypertension.

In 1998, the WHO,[11] developed the first definition of the metabolic syndrome and identified CAD as the primary clinical outcome. Under this definition, insulin resistance (or possible manifestations of insulin resistance) is a required component for the diagnosis. Insulin resistance is indicated by one of the following: Type 2 diabetes, Impaired fasting glucose, Impaired glucose tolerance and for those with normal fasting glucose, glucose uptake below the lowest quartile for background population under investigation under hyperglycemic,

euglycemic conditions. When insulin resistance is present, the diagnosis of the metabolic syndrome is established if two or more of the following are present: 1) Blood pressure - Antihypertensive medication and/or blood pressure ≥140 mm Hg/≥90 mm Hg; 2) Plasma triglycerides ≥150 mg/dL (1.695 mmol/L); 3) HDL cholesterol - Men <35 mg/dL (0.897 mmol/L) and Women <39 mg/dL (1.0 mmol/L); 4) Obesity Body mass index > 30 kg/m2 and/or waist-to-hip ratio > 0.9 inches in men and > 0.85 inches in women; 5) Renal function/Kidney disease Urinary albumin excretion rate ≥ 20 μg/min or albumin:creatinine ratio ≥ 30 mg/g.

The AACE,[11] uses the term 'insulin resistance syndrome' to describe a more comprehensive group of risk factors. Under the AACE definition, diagnosis of the metabolic syndrome depends on clinical judgment, because there is no minimum number of factors that result in having the syndrome.

Under the NCEP-ATP III,[11] guidelines, for a person to be diagnosed with metabolic syndrome, three or more of the following criteria must be fulfilled: Abdominal obesity (waist circumference) - Men >40 inches (>102 cm) and Women >35 inches (>88 cm); Triglycerides ≥150 mg/dL (1.695 mmol/L); HDL cholesterol - Men <40 mg/dL (1.036 mmol/L) and Women <50 mg/dL (1.295 mmol/L); Blood pressure ≥130/≥85 mm Hg; Fasting glucose ≥100 mg/dL (5.6 mmol/L). As per ATP-III, abnormalities in lipid profile include an LDL cholesterol > 130 mg/dl and total cholesterol > 200 mg/dl.

Even with the lack of a universally accepted definition for the metabolic syndrome, there is a wealth of well-designed studies that indicate patients with this syndrome are at increased risk for premature death as well as the development of CAD and diabetes. Individuals with the metabolic syndrome also are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer. People with the metabolic syndrome also have an increased all-cause (cardiac and non-cardiac related) mortality rate.

The pathogenesis of the metabolic syndrome is complex, poorly understood. The complicated interaction between metabolically active visceral adipose tissue and resultant insulin resistance is the most widely accepted theory. The presence of visceral obesity is thought to be athrogenic due to increased lipolysis and release of nonesterified FFAs. The elevated hepatic and plasma FFA concentrations result in abnormal gluconeogenesis or glucose dysregulation. Also, the increased levels of FFAs can increase vasoconstriction and increase systemic blood pressure. Other by-products of lipolysis include proinflammatory markers that damage the vascular system, such as angiotensinogen, adipsin, adiponectin, leptin, interleukin-6, and tumor necrosis factor–α (TNF-α. In addition to causing direct endothelial dysfunction, TNF-α also decreases the activity of lipoprotein lipase, which causes atherogenic dyslipoproteinemia or elevated triglycerides, decreased HDL, and pathologically small LDL particle size. As visceral obesity increases, so does the likelihood of developing insulin resistance. An insulin-resistant state will worsen proinflammatory lipolysis, blood pressure, and lipid metabolism. Like TNF-α, insulin resistance decreases lipoprotein lipase activity and results in dyslipidaemia, with a heightened risk for CAD.

The majority of individuals diagnosed with kind 2 diabetes mellitus (T2DM) are carrying excess weight. The rise in prevalence of this kind of diabetes in the United States and several other regions is closely associated with the general surge in obesity rates. The primary explanation for this link is the impact of fat on reducing tissue sensitivity, resulting in insulin resistance. Insulin resistance is a consistent characteristic of type 2 diabetes mellitus (T2DM), even in individuals with relatively normal body weight. However, the majority of persons who are

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resistant to insulin do not have diabetes. This is because people with normal β-cell activity are able to significantly boost their production of insulin to counteract the reduced sensitivity to insulin. T2DM may be defined as a state when insulin secretion is insufficient to counteract insulin resistance.

The American Diabetes Association 2012,[12] criteria for diagnosing Diabetes Mellitus are as follows:

Glycosylated Haemoglobin ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay (OR)

Fasting plasma glucose ≥ 126mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8hours (OR)

2-hour plasma glucose ≥ 200mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by the World Health Organisation, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water (OR)

In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200mg/dl (11.1mmol/l)

Those patients with Fasting plasma glucose between 100-125mg/dl are said to have Impaired Fasting glucose and 2-hour plasma glucose between 140-199, as impaired glucose tolerance. Patients having Glycosylated Haemoglobin between 5.7-6.4 are said to be in pre-diabetes state.

A study conducted in a clinical setting for Bipolar Out-patients revealed that the most frequently affected category was Endocrine, Nutritional, and Metabolic diseases, accounting for 13.6% of the clinical sample. This category encompasses conditions like diabetes, obesity, thyroid diseases, and hypercholesterolemia.[13] A research conducted in a hospital environment revealed that the occurrence of diabetes was notably greater among 345 bipolar patients who were admitted as in-patients and had either a mixed or manic subtype (9.9%) compared to the general population (3.4%).[14]

Diabetes may also influence the progression of bipolar disorder. people who have both bipolar illness and concomitant diabetes have a higher number of mental hospitalisations throughout their lifespan compared to people with bipolar disorder who do not have diabetes. The correlation between these two conditions highlights the need of doing diabetes screenings in individuals with bipolar disorder, especially because timely identification and commencement of therapy to regulate blood sugar levels might potentially avert consequences associated with diabetes. Diabetes is linked to the presence of cerebrovascular lesions affecting tiny cerebral arteries inside the brain tissue and causing localised infarctions. The occurrence of manic episodes may be more frequent in individuals with cerebral microvascular disease, which further emphasises the need of reducing diabetes-related problems in people diagnosed with bipolar disorder. The presence of metabolic syndrome with bipolar illness affects how the condition is manifested and progresses, as well as how it responds to treatment.[15]

MATERIALS AND METHODS

A cross-sectional research was conducted at the Department of Psychiatry from December 2011 to May 2012. A total of 50 consecutive individuals diagnosed with Bipolar Affective Disorder, according to the D.S.M.-IV-T.R. criteria, and aged between 18 and 65 years, were included in the research after providing written informed permission. Prior to the research, the institutional ethics committee granted ethical approval. This study included patients diagnosed with Bipolar Affective Disorder (in an episode of hypomania/mania/depression or in remission) according to the D.S.M.-IV-T.R. criteria, who were between the ages of 18 and 65 and willing to participate after providing written informed consent. The study excluded patients who declined to participate, patients under the age of 18 or over the age of 65, patients diagnosed with mental retardation, patients diagnosed with organic mood disorder, and patients with severe complications of diabetes mellitus or any other condition requiring intensive care.

Methodology

All patients who visited the outpatient service of the Psychiatry Department or were hospitalised to the Psychiatry ward at Yenepoya Medical College Hospital were included in the research after receiving an explanation of the procedure and providing informed permission. The diagnosis of Bipolar Affective Disorder was determined via the M.I.N.I. Plus assessment tool, which adheres to the diagnostic criteria outlined in the D.S.M.-IV-T.R.

The MINI Plus is a concise and organised diagnostic interview, collaboratively created by psychiatrists and doctors from the United States and Europe, specifically designed for identifying mental illnesses according to DSM IV and ICD 10 criteria. The administration process typically lasts about 15 minutes. The purpose of its invention was to fulfil the need for a concise but precise structured psychiatric interview that could be used in multi-center clinical trials and epidemiological investigations. The MINI Plus has strong reliability and validity when compared to the Structured Clinical Interview for DSM III R.

The diagnosis of Diabetes mellitus was established based on the criteria set out by the American Diabetic Association. HbA1c levels above 6.5%. The test must be conducted in a laboratory using an NGSP-certified technique that is standardised to the DCCT assay. The fasting plasma glucose level should be equal to or greater than 126mg/dl (7.0mmol/l). Fasting is characterised by the absence of caloric consumption for a minimum of 8 hours or a plasma glucose level of at least 200mg/dl (11.1mmol/l) during a two-hour oral glucose tolerance test (OGTT). The test should

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be conducted according to the guidelines provided by the World Health Organisation, use a glucose load consisting of 75g anhydrous glucose dissolved in water or an appropriate substitute. If a patient exhibits typical symptoms of high blood sugar or a severe high blood sugar episode, a random measurement of plasma glucose equal to or more than 200mg/dl (11.1mmol/l) is indicative. A distinct clinical proforma was used to document the clinical associations, socio-demographic information, physical examination observations, and laboratory investigation results. The blood samples underwent the following laboratory investigations: Tests were conducted to measure the levels of fasting blood sugar, post prandial blood sugar, glycosylated haemoglobin, fasting lipid, and thyroid profile.

Statistical Analysis

The data was inputted into Microsoft Excel and statistical analysis was conducted using the S.P.S.S. programme Version 11.5. The comparison of qualitative variables was conducted using the Chi-square test, and a p-value of less than 0.05 was considered statistically significant. The findings are shown in the format of pie charts, bar graphs, and tables.

RESULTS

Table 1 displays the categorization of patients according to their gender and presence of Metabolic syndrome. 60% of the patients were male, while the remaining 40% were female. The proportion of individuals who were admitted as in-patients and those who received treatment as out-patients. 88% of the individuals were admitted as in-patients, while the remaining 12% received outpatient care.18 percent of those diagnosed with Metabolic syndrome. [Table]

Table 2 displays the findings of the Blood sugar estimation. 80% of patients had normal levels of both fasting blood sugar and post-prandial blood sugar. 16% of the patients had Impaired Fasting glucose, whereas 20% showed Impaired Glucose tolerance. 4% of the patients had fasting blood sugar levels that fell within the diabetes range (equal to or more than 200mg/dl), but none of the patients showed post-prandial blood sugar levels in the diabetic range. 42% of patients exhibited Glycosylated Haemoglobin levels within the normal range, whereas 44% of patients had levels within the pre-diabetic range. 14% of patients had Glycosylated Haemoglobin levels that were within the diabetes range (>=6.5%). [Table 2]

Table 3 shows the results of the Fasting Lipid profile. 26% of the patients had Cholesterol levels above 200mg/dl whereas 74% had it in the normal range. 20% of patients had elevated L.D.L. levels and 80% had it in the normal range. 58% of patients had H.D.L. levels below 40mg/dl while 42% had above. [Table 3]

Table 4 shows the results of the Fasting Thyroid Function tests. 92% of patients had T3 levels in the normal range and 88% had T4 levels in the normal range. 4% of patients had elevated T3 and T4 and 4% and 8% of patients respectively had T3 and T4 levels below normal range 86% of patients had T.S.H. levels in the normal range. 10% of patients had elevated T.S.H. (>6.2) and 4% had lower levels of T.S.H. [Table 4]

Tables 4 and 5 show the results of waist/Hip ratio measurements in females and males. 60% of males and 45% of females had increased waist/hip ratio measurements while 40% and 55% respectively had it in the normal range. [Table 5]

Table 7 shows the correlation between a familial background of bipolar affective illness and increased levels of blood glucose. 62.5% of individuals with a positive family history had impaired fasting glucose, whereas 60% showed impaired glucose tolerance. Patients with elevated fasting blood sugar levels within the diabetic range had a confirmed familial predisposition to bipolar illness. 37.5% of individuals who did not have a family history had impaired fasting glucose, whereas 40% showed impaired glucose tolerance. The fasting and post-prandial blood sugars between the two groups yielded p-values of 0.523 and 0.884, respectively, indicating a lack of statistical significance. [Table 7]

Table 1: Basic profile of the participants

	Number	Percentage
Gender		
Male	30	60
Female	20	40
Patients		
In-Patients	44	88
Out-Patients	6	12
Metabolic syndrome		
Present	9	18
Absent	41	82

Table 2: Blood sugar estimation

	Frequency (n)	Percentage (%)
Fasting Blood Sugar (mg/dl)		
<=99	40	80
100-125 (impaired fasting glucose)	08	16
>=126 (diabetic)	02	04
Post-prandial Blood Sugar (mg/dl)		
<=139	40	80

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140-199 (impaired glucose tolerance)	10	20
>=200 (diabetic)	0	0
Glycosylated Haemoglobin (%)		
<5.7	21	42
5.7-6.4 (pre-diabetic)	22	44
>=6.5 (diabetic)	07	14

Table 3: Fasting Lipid Profile

	Frequency	Percentage
Cholesterol (mg/dl)		
>200	13	26
<200	37	74
L.D.L. (mg/dl)		
>130	10	20
<130	40	80
H.D.L. (mg/dl)		
<40	29	58
>40	21	42

Table 4: Thyroid Function tests

	Frequency	Percentage
T3 (ng/ml)		
<0.69	02	04
0.69-2.02	46	92
>2.02	02	04
T4 (Ug/dl)		
<4.4	04	08
4.4-11.6	44	88
>11.6	02	04
T.S.H.(mIU/l)		
<0.4	02	04
0.4-6.2	43	86
>6.2	05	10

Table 5: Waist/hip ratio (males)

	Frequency	Percentage
<=0.9	12	40
>0.9	18	60
Total	30	100

Table 6: Waist/hip ratio (females)

	Frequency	Percentage
<=0.85	11	55
>0.85	09	45
Total	20	100

Table 7: Family history of BPAD and Blood sugars

	Family history of BPAD		Statistics
	Yes (%)	No (%)	
Fasting Blood Sugar (mg/dl)			
<=99	60	40	P=0.523
100-125 (Impaired fasting glucose)	62.5	37.5	
>126 (diabetic)	100	0	
Post-prandial Blood Sugar (mg/dl)			
<=139	62.5	37.5	P=0.884
140-199 (Impaired glucose tolerance)	60	40	
>=200 (diabetic)	0	0	

DISCUSSION

Persons diagnosed as having bipolar disorder experience more co-occurring general medical conditions--especially cardiovascular disease and conditions related to metabolic syndrome, for example, diabetes--compared with those without bipolar disorder or other chronic mental illnesses.[16] This study was done to assess the presence of Diabetes Mellitus in patients with Bipolar Affective Disorder. The sample size of my study was 50. This is comparable to many previous studies done on the same subject,[17,18] Also, the study included bipolar patients in the age group 18- 65 years, which is comparable to the age group analysed in previous studies,[17,19]

In the current study, 18% of patients with bipolar disorder had satisfied W.H.O. criteria for metabolic syndrome, of which 12% were males and 6% were females. We also found that 26% of the patients had

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Cholesterol levels above 200mg/dl, 20% of patients had elevated L.D.L. levels and 58% of patients had H.D.L. levels below 40mg/dl. Persons diagnosed as having bipolar disorder experience more co-occurring general medical conditions--especially cardiovascular disease and conditions related to metabolic syndrome, for example, diabetes--compared with those without bipolar disorder or other chronic mental illnesses.[16] There is also increasing evidence of an association between bipolar disorder and the metabolic syndrome and its components. In patients with bipolar disorder, a prevalence rate of 25% for American patients recruited between 1995 and 2001 was reported,[21] whereas in an earlier study, a prevalence rate of 35% was reported for 175 patients recruited in the period between 1991 and 2000.[21] A later study showed a prevalence rate of 45% for 171 patients recruited from 2003 to 2004.[22] In a study from India conducted at Chandigarh, 200 patients with bipolar disorder were evaluated for the presence of metabolic syndrome. Around 80 patients (40%) were diagnosed with the same though the criteria used was different from the one used in our study.[23] In a retrospective Danish national registry study with bipolar individuals, it was found that 49% had abdominal obesity, 48% were hypertriglyceridemic or were on a cholesterol lowering medication, 23% had low H.D.L. cholesterol, 39% had high blood pressure, 8% were high in fasting glucose or were on anti-diabetic medication and 30% met criteria for metabolic syndrome.[25] Compared to these studies, the rate of metabolic syndrome in this study is significantly lower. Further studies need to be done to ascertain the exact mechanisms and prevalence in Indian patients with Bipolar disorder.

In our study, it was found that only 8% of patients had abnormalities in T3 levels and 12% in T4 levels. Out of which, 4% of patients had elevated T3 and T4 and 4% and 8% of patients respectively had T3 and T4 levels below normal range. Also, only a very small percentage, i.e., 14% of patients had abnormal T.S.H. levels, 10% of patients had elevated T.S.H. (>6.2) and 4% had lower levels of T.S.H. A group of investigators at Copenhagen conducted prospective cohort studies utilising historical data from Danish case registers to determine the association between thyroid and affective disorders. In separate reports, it was demonstrated that patients hospitalised with bipolar disorder tended to be at a greater risk of re-admission with hyperthyroidism than controls,[25] while patients hospitalised with hyperthyroidism were at greater risk of readmission with depressive disorder or bipolar disorder than controls.[26] Finally, patients hospitalized with hypothyroidism also had a greater risk of readmission with depression or bipolar disorder, than control patients. These results are contradictory to the ones found in our study. On the other hand, quite a few other investigations of medical comorbidity among patients with bipolar disorder have not found a significant increase in the prevalence of thyroid disorders. In an extensive review on bipolar disorder and thyroid abnormalities, the reviewer concluded that, even though both hyperthyroidism and hypothyroidism are associated with changes in mood; overt bipolar disorder is uncommon in thyroid dysfunction.[27]

Limitations of this study

The study's sample size was limited to 50 participants diagnosed with bipolar illness. This has the potential to impact the generalizability of the findings. Increasing the sample size would provide more definitive and conclusive results. This research has a cross-sectional design and lacks a control group. The inclusion of a meticulously chosen control group would enhance the validity of the produced outcomes. The research did not gather information on the specific drugs that the participants were taking. Therefore, the potential impact of medications such as anti-psychotics and mood stabilisers on the occurrence of diabetes mellitus, dyslipidemia, and metabolic syndrome was not considered. Furthermore, this research did not take into consideration the impact of Lithium, a commonly used mood stabiliser, on the occurrence of thyroid problems.

CONCLUSION

We concluded that 26% of the patients had Cholesterol levels above 200mg/dl, 20% of patients had elevated L.D.L. levels and 58% of patients had H.D.L. levels below 40mg/dl. With reference to the thyroid status of the bipolar sample, it was found that only 8% of patients had abnormalities in T3 levels, 12% in T4 levels and 14% of patients had abnormal T.S.H. levels.

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