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Original Research Article

EVALUATION OF THE CLINICAL CORRELATES OF PATIENTS WITH BIPOLAR DISORDER HAVING DIABETES MELLITUS: A TERTIARY HOSPITAL BASED STUDY

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Abstract

Background: Bipolar illness is a collection of enduring mental conditions characterised by fluctuations in mood and energy levels. Although the acute phase of the disorders is characterised by intense psychological symptoms, the chronic course is often influenced by a growing load of concurrent medical problems. The prevalence of diabetes mellitus in individuals with bipolar illness is notably high, however the underlying reasons remain unclear. Treatment and lifestyle variables may have a substantial impact, and some studies also propose a connection in the underlying mechanisms and risk factors. **Aim:** To study the clinical correlates of patients with Bipolar Disorder having Diabetes Mellitus. **Materials & Methods:** All consecutive In-patients and Out-patients diagnosed with Bipolar Affective Disorder, as per D.S.M.-IV-T.R. criteria, between the age-groups of 18-65 years were recruited for the study, following written informed consent. Ethical clearance was obtained from the institutional ethics committee prior to the study. 50 patients were included in this study. **Results:** 50% of patients who had onset of illness below or at 30 years of age and above 30 years of age had impaired fasting glucose and diabetic (>126mg/dl) levels. P value of 0.394 was got showing no statistically significant difference between the groups. 60% of patients who had onset of illness after 30years of age had impaired glucose tolerance, compared to 40% who had earlier onset of illness. P value of 0.0394 was obtained which showed statistically significant elevation of post-prandial sugars in those who had later onset of illness. 25% of patients who had a history of suicide attempt in the past had impaired fasting glucose and 30% had impaired glucose tolerance. 50% of patients in this group had fasting blood sugar in the diabetic range. In comparison, 75% of patients who had no history of suicide attempts had impaired fasting glucose and 70% had impaired glucose tolerance. P values for both groups were 0.495 and 0.377 respectively showing no statistical significance between suicide and elevated blood sugars. **Conclusion:** In conclusion, this was a cross- sectional, tertiary hospital based study with a convenience sampling method which chiefly attempted to look for presence of diabetes mellitus in 50 patients with bipolar affective disorder. MINI Plus was used to establish the diagnosis and blood tests were done to detect diabetes, which was diagnosed by the ADA criteria. The chief result of the study is that we found 4 – 14 % of patients with bipolar disorder had diabetes, the different rates yielded by the different blood investigations studied. Positive associations were found between later age of onset of bipolar disorder and elevated sugar levels.

INTRODUCTION

Mood is a pervasive and sustained feeling tone that is experienced internally and that influences a person's behaviour and perception of the world. Patients with elevated mood demonstrate expansiveness, flight of ideas, decreased sleep and grandiose ideas whereas patients with depressed mood experience a loss of energy and interest, feelings of guilt, difficulty in concentrating, loss of appetite and death wishes and

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suicidal ideation. Other signs and symptoms of mood disorders include change in activity level, cognitive abilities, speech and vegetative functions such as sleep, appetite, sexual activity and other biological rhythms. These disorders virtually always result in impaired interpersonal, social and occupational functioning. Patients with both manic and depressive episodes or patients with manic episodes alone are said to have Bipolar disorder. Increasingly the conventional figure of 1 % for Bipolar disorders in the general population is being challenged and there are now convincing data that this group of disorders may account for 5% of the general population and up to 50% of all depressions. Despite the availability of effective treatments, many persons with mood disorders are disabled, and rates of suicide are high in young and the elderly. An alarming increase of suicide rates among middle-aged women has been recently reported.

Bipolar Affective disorder is treated with a combination of pharmacological and non-pharmacological methods. Pharmacological management includes use of mood stabiliser agents (Lithium, Carbamazepine, Sodium Valproate, Lamotrigine etc.), anti-depressants and anti-psychotics. As per the D.S.M.-I.V.-T.R. (American Psychiatric Association),[1] there are six separate criteria sets for Bipolar I disorder: single manic episode, most recent episode hypomanic, most recent episode manic, most recent episode mixed, most recent episode depressed and most recent episode unspecified. Bipolar I disorder, single manic episode is used to describe individuals who are having the first episode of mania. The remaining criteria sets are used to specify the nature of the current (or most recent) episode in individuals who have had recurrent mood episodes. A manic episode is diagnosed when symptoms last at least for one week (or any duration if hospitalisation is necessary). A hypomanic episode is diagnosed if symptoms last at least for four days. A mixed episode is diagnosed when criteria for both manic and depressive symptoms are met nearly every day during at least a one-week period. A depressive episode is diagnosed when symptoms have been present at least for a period of two weeks.[2]

Diabetes can be defined as disorders of nutrient metabolism that result in abnormalities in circulating glucose and, frequently, lipids. These abnormalities confer an increased risk for vascular diseases, infectious complications, and other morbidities. Although a number of distinct syndromes exist, diabetes is generally caused by impaired insulin secretion with or without abnormal sensitivity to insulin action. The vast majority of affected patients have either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM), and although these diseases share several clinical features, their pathogenesis is markedly different. Of the two types of diabetes, T2DM is eight to nine times more common and is closely related to obesity, a problem that is on the rise worldwide. Although T1DM was previously called juvenile-onset diabetes and T2DM was called adult-onset diabetes, it is now clear that both diseases affect people from childhood to older age. As the incidence of both types of diabetes has increased markedly since the 1980s, diabetes will be one of the major public health burdens for the foreseeable future. Type 1 diabetes arises as a result of autoimmune destruction of the insulin-producing beta-cells of the pancreas; referred to in the literature and in clinical settings as “childhood” or “juvenile-onset” diabetes or “insulin-dependent” diabetes mellitus. Patients with Type 1 diabetes are by definition insulin dependent. When insulin is absent, hepatic glucose production is uncontrolled, and blood glucose levels rise. Glucose uptake by muscle and other peripheral tissues is minimal without insulin stimulation. Without inhibition by insulin, adipocytes release fatty acids at a brisk rate, and these fatty acids are metabolized in the liver to ketone bodies.[3] Persons with T1DM typically present with symptoms of hyperglycemia such as polyuria and polydipsia resulting from glucosuria and osmotic diuresis. Weight loss is almost invariable and results from wasting of glucose calories lost with glucosuria as well as impaired nutrient storage in the absence of insulin. Only insulin therapy will ultimately be effective in T1DM patients, and delay in its provision can lead to serious consequences. Type 2 diabetes is the most prevalent form of diabetes; also referred to as non-insulin-dependent diabetes, adult-onset diabetes, or obesity-related diabetes. It is caused by the combination of impaired insulin secretion and insulin resistance. T2DM is the most common form of diabetes, accounting for approximately 90% of cases. Indeed, it is currently estimated that the number of patients with undiagnosed T2DM is one-third against the number of known cases. Although trends in the industrialized world have been similar, there are now alarming increases in rates of T2DM in countries such as China and India, where the disease was previously rare.

Most patients with T2DM are overweight, and the increase in this form of diabetes in the United States and many other parts of the world is strongly linked to the overall increase in obesity. This connection is most commonly explained by the effects of obesity in decreasing tissue sensitivity, thus causing insulin resistance. Insulin resistance is an invariable component of T2DM, even among patients with relatively normal body weight. However, most insulin-resistant people are not diabetic, because individuals with normal β-cell function increase their insulin output many fold to compensate for decreased insulin sensitivity. In fact, T2DM can be simply conceptualized as a condition in which insulin secretion cannot compensate for insulin resistance.[4]

In a study conducted in a Bipolar Out-patient clinical setting, it was found that the category most commonly affected was that of Endocrine, Nutritional and Metabolic diseases (13.6% of the clinical sample) which includes diseases such as diabetes, obesity, thyroid diseases and hypercholesterolemia.[5] In a study based on an In-

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patient setting it was found that prevalence of diabetes was significantly higher in 345 hospitalised bipolar patients with mixed or manic subtype (9.9%) than in the overall population (3.4%). (4) Comorbidity refers to the occurrence of two syndromes in the same patient. Defined literally, every pair of syndromes where the diagnosis of one does not categorically exclude the diagnosis of the other is potentially comorbid.[4] The presence of medical comorbidities in patients with Bipolar Disorder is an anticipated complication of a life long illness.[5] Having a chronic medical disorder diagnosed by a physician was associated with less successful employment outcomes, greater dependency on others for assistance, and higher utilization of mental health care services including hospitalization.[6] There are several causal pathways that may be salient to the overlap between bipolar disorder and medical comorbidity. Patients with bipolar disorder have many risk factors-such as insufficient access to primary and preventive health care, lower socioeconomic status, poor adherence to medical regimes, smoking, habitual inactivity, substance abuse, comorbid binge-eating disorder, adverse childhood experiences and high caloric intake. Moreover, affective disease activity is coupled to immunoinflammatory and counterregulatory hormone activation which may result in end-organ allostasis. Iatrogenic causes are also possible-for example, hypothyroidism (lithium), diabetes mellitus type 2 (atypical anti-psychotics) and polycystic ovarian disease (divalproex).[6]

MATERIALS AND METHODS

A Cross-sectional study was done in the department of Psychiatry from December 2011 to May 2012. All consecutive In-patients and Out-patients diagnosed with Bipolar Affective Disorder, as per D.S.M.-IV-T.R. criteria, between the age-groups of 18-65 years were recruited for the study, following written informed consent. Ethical clearance was obtained from the institutional ethics committee prior to the study. 50 patients were included in this study.

Inclusion Criteria

- Those patients willing to participate in the study following a written informed consent.
- Male and female patients between the age group of 18-65 years, diagnosed as having Bipolar Affective Disorder (in an episode of hypomania/mania/depression or in remission) as per D.S.M.-IV-T.R. criteria.

Exclusion Criteria

- Those patients not willing to participate.
- Patients below 18years of age or above 65years of age.
- Patients diagnosed with Mental Retardation.
- Patients diagnosed with Organic Mood Disorder.
- Patients with serious complications of diabetes mellitus or any other condition necessitating intensive care.

Methodology

All patients attending the outpatient service of the Psychiatry Department or admitted to the Psychiatry ward, Yenepoya Medical College Hospital were enrolled into the study after explaining the protocol and taking informed consent. The diagnosis of Bipolar Affective Disorder was made using M.I.N.I. Plus based on the D.S.M.-IV-T.R. criteria.

The MINI Plus is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM IV and ICD 10 psychiatric disorders. It takes approximately 15 minutes to administer. It was designed to meet the need for a short but accurate structured psychiatric interview for multi-centre clinical trials and epidemiological studies. The MINI Plus has been found to have good reliability and validity when measured against the Structured Clinical Interview for DSM III R.[7]

The diagnosis of Diabetes mellitus was made as per the American Diabetic Association criteria

1. 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
2. Fasting plasma glucose ≥ 126mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8hours or
3. 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
4. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200mg/dl (11.1mmol/l)

A separate clinical proforma was used for recording the clinical correlates, socio-demographic data, physical examination findings and the laboratory investigations reports.

The following laboratory investigations were done on the blood samples: Fasting Blood Sugar, Post Prandial Blood Sugar and Glycosylated Haemoglobin level and Additional blood tests were done which included fasting lipid and thyroid profile.

Statistical Analysis

The collected data was entered in M.S. Excel and statistical analysis was done by using S.P.S.S. software Version 11.5. The comparison of qualitative variables was done by using statistical test Chi-square test and a p value <0.05 was taken as statistically significant. The results are presented in the form of pie-charts, bar diagrams and tables.

RESULTS

A total of 50 patients were included in the study

Figure 1 above shows the distribution of patients based on gender. 60% of patients were males and 40% were females.

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Figure 2 shows the percentage of patients who were In-patients and Out-patients. 88% of patients were In-patients and 12% were Out-patients.

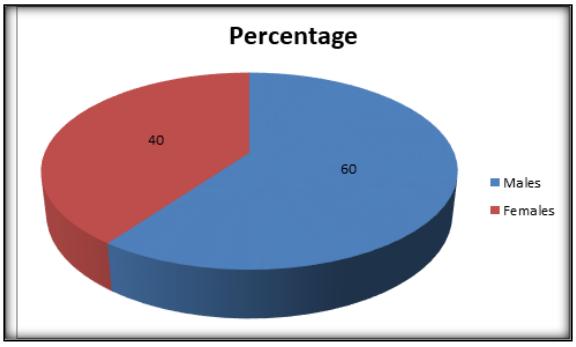

Figure 1: Gender distribution

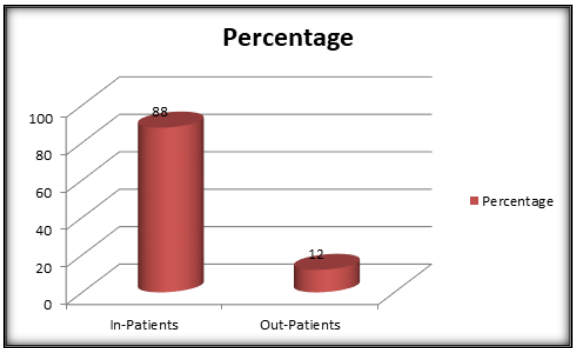

Figure 2: In-Patients/Out-Patients

Table 1 shows the results of the Blood sugar estimation. 80% of patients had Fasting blood sugar and Post-prandial blood sugars in the normal range. 16% of patients had Impaired Fasting glucose and 20% had Impaired Glucose tolerance. 4% of patients had Fasting blood sugars in the diabetic range (>=200mg/dl) and no patients had Post-prandial blood sugars in the diabetic range. 42% of patients had Glycosylated Haemoglobin in the normal range and 44% of patients had it in pre-diabetic range. 14% of patients had Glycosylated Haemoglobin in the diabetic range (>=6.5%). [Table 1]

Table 2 shows the B.M.I. values (calculated as per weight (in kg)/height (m2). 68% of patients had B.M.I. in the normal range while 20% were overweight and 2% were obese. 10% of patients were underweight. [Table 2]

Table 3 shows the association between age of onset and elevated Blood sugars. 50% of patients who had onset of illness below or at 30 years of age and above 30 years of age had impaired fasting glucose and diabetic (>126mg/dl) levels. P value of 0.394 was got showing no statistical significance between the groups. 60% of patients who had onset of illness after 30years of age had impaired glucose tolerance, compared to 40% who had earlier onset of illness. P value of 0.0394 was obtained which showed statistically significant elevation of post-prandial sugars in those who had later onset of illness. [Table 3]

Table 4 shows the association between psychiatric comorbidity and blood sugars. 50% of patients in both groups had impaired fasting glucose and impaired glucose tolerance. respectively. Patients who had blood sugars in the diabetic range as per fasting blood sugar values had no psychiatric comorbidity. P values of 0.287 and 0.123 were obtained for fasting and post-prandial blood sugars which shows no statistical significance between the two groups. [Table 4]

Table 5 shows the association between suicide and blood sugars, B.M.I. and waist/hip ratio. 25% of patients who had a history of suicide attempt in the past had impaired fasting glucose and 30% had impaired glucose tolerance. 50% of patients in this group had fasting blood sugar in the diabetic range. In comparison, 75% of patients who had no history of suicide attempts had impaired fasting glucose and 70% had impaired glucose tolerance.

P values for both groups were 0.495 and 0.377 respectively showing no statistical significance between suicide and elevated blood sugars. 30% of patients who attempted suicide were overweight and all patients who were obese had a history of suicide attempt. In comparison, 70% of patients who had no history of suicide attempts were overweight. P value of 0.161 was got which shows no statistical significance between increased B.M.I. and history of suicide attempts. 18.5% of patients who attempted suicide had an increased waist/hip ratio as compared to 81.5% in those who had no suicide attempts. P value of 0.777 was obtained which showed no statistical significance between increased waist/hip ratio and history of suicide attempts. [Table 5]

Table 1: 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
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

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Table 2: Body Mass Index

	Frequency	Percentage
<18.5 (underweight)	05	10
18.5-24.9 (normal)	34	68
25.0-29.9 (overweight)	10	20
>30 (obese)	01	02
Total	50	100

Table 3: Age of onset of bipolar disorder and Blood sugars

	Age of onset		Statistics
	<=30 (%)	>30 (%)	
Fasting Blood Sugar (mg/dl)			
<=99	72.5	27.5	P=0.394
100-125 (Impaired fasting glucose)	50	50	
>126 (diabetic)	50	50	
Post-prandial Blood Sugar (mg/dl)			
<=139	75	25	P=0.034*
140-199 (Impaired glucose tolerance)	40	60	
>=200 (diabetic)	0	0	

Table 4: Psychiatric comorbidity in bipolar disorder and Blood sugars

	Psychiatric comorbidity		Statistics
	Yes (%)	No (%)	
Fasting Blood Sugar (mg/dl)			
<=99	27.5	72.5	P=0.287
100-125 (Impaired fasting glucose)	50	50	
>126 (diabetic)	0	100	
Post-prandial Blood Sugar (mg/dl)			
<=139	25	75	P=0.123
140-199 (Impaired glucose tolerance)	50	50	
>=200 (diabetic)	0	0	

Table 5: Suicide and Blood Sugars, B.M.I. and Waist/Hip ratio

	Suicide		Statistics
	Yes (%)	No (%)	
Fasting Blood Sugar (mg/dl)			
<=99	17.5	82.5	P=0.495
100-125 (Impaired fasting glucose)	25	75	
>126 (diabetic)	50	50	
Post-prandial Blood Sugar (mg/dl)			
<=139	17.5	82.5	P=0.377
140-199 (Impaired glucose tolerance)	30	70	
>=200 (diabetic)	0	0	
B.M.I.			
<18.5 (underweight)	16.7	83.3	P=0.161
18.5-24.9 (normal)	15.2	84.8	
25.0-29.9 (overweight)	30	70	
>30 (obese)	100	0	
Waist/Hip ratio			
High	18.5	81.5	P=0.777
Normal	21.7	78.3	

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.[8] 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.[9, 10] Also, the study included bipolar patients in the age group 18- 65 years, which is comparable to the age group analysed in previous studies.[9, 11]

In this study, it was found that 4% of patients had Diabetes Mellitus according to Fasting blood sugar levels and 14% of patients according to Glycosylated Haemoglobin levels. These findings are similar to the findings of a study on 203 bipolar patients followed up over 10 years, where 10% of patients with Bipolar Disorder developed diabetes.[11] Similarly, another study reported that 9.9% of 357 patients aged 20- 74 years with bipolar disorder had diabetes mellitus.[8] This study was conducted in hospitalised bipolar patients. In our study too, 88% of patients were in-patients and the findings of both studies are similar. However, some other studies have reported higher rates. One study reported a rate of 26%,[12] but the patients included were in the age group of 50- 74

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years and on treatment. Another study reported a rate of 38% (10) in 42 unmedicated bipolar individuals in the age group of 18- 71 years.

In this study, no significant association was found between age of onset of bipolar disorder and elevated fasting blood sugars but statistically significant association was found between later onset of Bipolar disorder (after 30years of age) and elevated post-prandial blood sugars (p=0.0394). Some studies have stated that age at first hospitalisation and duration of psychiatric disorders was similar in patients with Bipolar disorder with and without co-morbid Diabetes mellitus.[8] Another has reported that lifetime axis 1 comorbidity was associated with earlier age at onset of affective symptoms and syndromal bipolar disorder.[13] However, we were unable to find any studies that have looked specifically at the association between age of onset of bipolar disorder and diabetes mellitus. One of the reasons for the higher PPBS with later age of onset in our study could be due to the higher age of these subjects, as the risk of diabetes increases as a person grows older. Akin to this, in one study previously conducted, the authors found that 38 % of 42 patients with bipolar disorder in the age group 18 -71 years had a hyperglycaemic response on OGTT. When the same test was done only on those in the age group 48 – 86 years, it was found that 53% demonstrated a hyperglycaemic response.[10]

In this study, no significant association was found between presence of psychiatric comorbidities and elevated fasting or post-prandial blood sugars (p values of 0.287 and 0.123 respectively). One study has reported comorbidity rates of 65% of at least one comorbid lifetime axis 1 disorder in 288 Bipolar disorder patients.[13] However, to the best of our knowledge, no study has analysed the relationship between comorbidity in bipolar disorder and chances of developing diabetes. Further studies need to be done on whether presence of increased comorbidities will be associated with greater risk of developing diabetes mellitus.

In this study, no significant association was found between a past history of suicide attempts in bipolar patients and elevated fasting or post-prandial blood sugars (p values of 0.495 and 0.377 respectively). Suicide rates among patients diagnosed with BD (mostly type I), as well as in severe forms of recurrent MDD, are much higher than in the general population, and substantially greater than in other psychiatric, substance use or general medical disorders. In BD, this risk is approximately 400-1400 per 100,000 per year (approximately 0.9% per year), or 25-90-times higher than the general population rate of 0.015% per year.[14] It has also been reported that young men with insulin-dependent diabetes mellitus were at higher risk of suicide and concluded that suicide may be underestimated as a cause of death among such patients.[15] Although the association between diabetes and depression is clearly delineated, this is not true for the association between diabetes and suicide risk. Several reports on suicide risk have presented case histories of patients with diabetes. In a follow up study of a cohort of Taiwanese patients with diabetes, 0.8% of the deaths were found to be due to suicide.[16] Hence, several studies have found an association between affective disorders and suicide, as also between diabetes and suicide. However, we have been unable to find any studies that look specifically at association between suicide attempts and diabetes mellitus in patients with Bipolar disorder. Further research would need to be done in this area.

In our study, it was found that 30% of patients who attempted suicide were overweight and all patients who were obese had a history of suicide attempt. However, there was no statistical significance between increased B.M.I. and history of suicide attempts. (p=0.161). It was also found that only 18.5% of patients who attempted suicide had an increased waist/hip ratio. Hence, no statistical significance was found between increased waist/hip ratio and history of suicide attempts (p=0.777). A previous study that looked for this association was done on 255 patients with bipolar disorder and it was found that over 30% were obese. It was also found that obese patients were nearly twice as likely to have a history of suicide attempts.[17]

Limitations of this study

The sample size of our study included only 50 patients with bipolar disorder. This could affect the generalisation of the results. A larger sample size would give more conclusive and definite results. The design of this study is cross-sectional and does not include a control group. A carefully selected control group would lend credibility to the results generated. The details of the medications the patients were on were not collected as part of the study. Hence the contribution of drugs (anti-psychotics, mood stabilisers) to the development of diabetes mellitus, dyslipidemia and metabolic syndrome could not be taken into account.

CONCLUSION

In conclusion, this was a cross- sectional, tertiary hospital based study with a convenience sampling method which chiefly attempted to look for presence of diabetes mellitus in 50 patients with bipolar affective disorder. MINI Plus was used to establish the diagnosis and blood tests were done to detect diabetes, which was diagnosed by the ADA criteria. The chief result of the study is that we found 4 – 14 % of patients with bipolar disorder had diabetes, the different rates yielded by the different blood investigations studied. Positive associations were found between later age of onset of bipolar disorder and elevated sugar levels. We could not establish a direct relation between family history of bipolar disorder, psychiatric comorbidity or suicide attempts in these patients and diabetes.

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