Review Paper

Clinical Features of Bipolar Disorder With and Without Comorbid Diabetes Mellitus

Martina Ruzickova, MD[1], Claire Slaney, RN[2], Julie Garnham, RN, BN[3], Martin Alda, MD, FRCPC[4]

Objective: Several papers have reported higher prevalence of diabetes mellitus (DM) type 2 in patients suffering from bipolar disorder (BD). The possible links between these 2 disorders include treatment, lifestyle, alterations in signal transduction, and possibly, a genetic link. To study this relation more closely, we investigated whether there are any differences in the clinical characteristics of BD patients with and without DM.

Method: We compared the clinical data of 26 diabetic and 196 nondiabetic subjects from The Maritime Bipolar Registry. Subjects were aged 15 to 82 years, with psychiatric diagnoses of BD I (n = 151), BD II (n = 65), and BD not otherwise specified (n = 6). The registry included basic demographic data and details on the clinical course of bipolar illness, its treatment, and physical comorbidity. In a subsequent analysis using logistic regression, we examined the variables showing differences between groups, with diabetes as an outcome variable.

Results: The prevalence of DM in our sample was 11.7% (n = 26). Diabetic patients were significantly older than nondiabetic patients ($P < 0.001$), had higher rates of rapid cycling ($P = 0.02$) and chronic course of BD ($P = 0.006$), scored lower on the Global Assessment of Functioning Scale ($P = 0.01$), were more often on disability for BD ($P < 0.001$), and had higher body mass index ($P < 0.001$) and increased frequency of hypertension ($P = 0.003$). Lifetime history of treatment with antipsychotics was not significantly associated with an elevated risk of diabetes ($P = 0.16$); however, the data showed a trend toward more frequent use of antipsychotic medication among diabetic subjects.

Conclusions: Our findings suggest that the diagnosis of DM in BD patients is relevant for their prognosis and outcome.

(Can J Psychiatry 2003;48:458–461)

Information on funding and support and author affiliations appears at the end of the article.

Clinical Implications

- Bipolar disorder (BD) patients with comorbid diabetes mellitus (DM) had a more severe course of BD and worse outcome.
- There is a higher socioeconomic burden in relation to comorbid DM in BD.
- The use of antipsychotic medication was not significantly associated with risk of DM in this sample.

Limitations

- The study groups were not matched for age or sex.
- The diabetic group was older.
- The study design was cross-sectional.

Key Words: *bipolar disorder, diabetes mellitus, comorbidity, clinical correlates, clinical characteristics, clinical course*

It has been recognized that bipolar disorder (BD) is associated with an increased risk of diabetes mellitus (DM), type 2 in particular. Since the second half of the last century, several researchers have investigated abnormalities in glucose metabolism among patients with manic depression, either in relation to the effects of lithium (1–3) or with respect to alterations in glucose metabolism during and outside of illness episodes (4,5). These studies were based mostly on the evidence of changes in glucose metabolism following lithium administration or on previously reported disturbances in glucose metabolism observed in psychiatric populations. Despite initial evidence, the first study that systematically examined the prevalence of DM in patients with manic depression appeared only in 1980 (6); it was followed by 2 additional papers in subsequent years (7,8). All 3 studies used the chart-review method, and all found increased rates of DM in BD patients. In particular, Lilliker found the prevalence of DM to be 10% in 203 patients with manic depression, while the expected prevalence for the sample was 2% (6). Cassidy and others reported a DM prevalence of 9.9% in a sample of 345 BD patients, compared with a prevalence of 3.4% expected for the general population (7). In a small sample of 53 patients, Regenold and others found DM in 26% of BD I patients, while the expected rate was 13% (8). The mean age of subjects in this study was higher than in the studies by Lilliker and Cassidy and others, which accounts for the higher observed (as well as expected) DM rates. The reverse relation—a higher frequency of BD in subjects with DM—has been shown as well. Lustman and others found a prevalence of 5.3% for mania and atypical BD in patients with DM type 2 (9). This is significantly higher than the lifetime prevalence of BD in the general population, which is usually estimated at 1%.

There are many possible links between these 2 disorders, including lifestyle, medication treatment, hypothalamo–pituitary–adrenocortical (HPA) axis dysregulation, and dysfunction at the signal transduction and (or) genetic level. The growing evidence of glucose abnormalities in BD patients led us to study the link between the 2 disorders more systematically. In this paper we examine differences in the clinical characteristics of BD patients who have and who do not have comorbid DM.

Methods

Subjects

All subjects were recruited through the Maritime Bipolar Registry, a community-based project carried out throughout the Maritime Provinces of Canada. At the time of the analysis, the Registry included data from 151 subjects diagnosed with BD I, 65 with BD II, and 6 with BD not otherwise specified (NOS); which gave us a total sample of 222 patients with BD.

Patients for the Registry were referred by their psychiatrists. All consenting subjects were interviewed in person and met the DSM-IV criteria for BD (10). Interviews were carried out by experienced physicians or trained research nurses. For each proband, the following information was collected at interview and from the patient's chart: basic demographic characteristics, height, and weight; details of the clinical presentation (including onset-age of mania and depression, psychiatric comorbidity, history of suicidal behaviour, and psychosis with episodes); treatment details; and details of medical comorbidity (including hypertension, thyroid disorder, and DM). Ethnically, most participants were of Irish, Scottish, or French Acadian origin.

Medical comorbidity, including DM, was ascertained based on previous diagnosis and evidence of treatment for each selected medical condition. Of the 222 subjects, 26 had comorbid DM (25 had DM type 2, and 1 had DM type 1).

Statistical Analysis

We analyzed the data using chi-square test for categorical and Mann–Whitney *U*-test for continuous variables. For variables contributing to between-group differences, we performed stepwise logistic regression with DM as a dependent (outcome) variable, and sex, age, body mass index (BMI), treatment with antipsychotics, and presence of hypertension as independent variables.

Results

The prevalence of DM in our sample was 11.7% (26/222 subjects; 95%CI, 7.8% to 16.7%). The 2 groups were not significantly different with respect to sex distribution: there were 72 men and 124 women without DM and 14 men and 12 women with DM. Probands with DM were significantly older than those without DM. The average ages were 52.5 years (SD 9.6) for subjects with comorbid DM and 42.8 years (SD 12.3) for subjects with BD and no DM. The distributions of diagnoses were similar in the 2 groups. In the group with comorbid DM, 17 subjects had BD I, 8 had BD II, and 1 had BD NOS. Among subjects without DM, 134 had BD I, 57 had BD II, and 5 had BD NOS (see Table 1).

Table 1 presents the differences between groups. In terms of the clinical course of BD, when compared with nondiabetic subjects, subjects with comorbid DM more often had a chronic pattern ($\chi^2 = 7.7$, df = 1, $P = 0.006$), significantly more rapid cycling ($\chi^2 = 5.7$, df = 1, $P = 0.02$), and lower scores on the Global Assessment of Functioning (GAF) Scale ($U = 1701$, $P = 0.01$).

Disability rates for BD were also significantly different between the 2 groups. Eighty-one per cent of individuals with comorbid DM were on long-term disability, compared with only 30 % of probands without DM ($\chi^2 = 26.9$, df = 1, $P < 0.001$). The whole sample showed higher-than-average BMI

(29.5, SD 6.4). Subjects with comorbid DM had higher BMI, with a mean in the obese range (33.7, SD 6.0), compared with nondiabetic subjects, who were on average in the overweight range (28.8, SD 6.3). In agreement with the generally accepted association of hypertension and DM type 2, the group with DM had a higher risk of hypertension as well (χ^2 = 8.9, df = 1, P = 0.003).

We were not able to find significant between-group differences in treatment with antipsychotics (χ^2 = 1.9, df = 1, P = 0.16), nor was the use of antipsychotic medication correlated with any of the variables. However, there was a trend toward higher use of antipsychotics in the group with DM.

In the stepwise logistic regression analysis, the only independent variables associated with a diagnosis of DM were age (χ^2 = 16.5, df = 1, P < 0.001) and BMI (χ^2 = 10.9, df = 1, P = 0.001).

Table 1 Demographic and clinical data of BD patients with and without comorbid DM

Variable	BD (n = 196)	BD + DM (n = 26)	Statistic	P
Age: mean (SD)	42.8 (12.3)	52.5 (9.6)	U = 3789	< 0.001
Sex (men : women)	72 : 124	14 : 12	χ^2 = 2.8	0.09
Diagnosis			χ^2 = 0.2	0.91
BD I	134	17		
BD II	57	8		
BD NOS	5	1		
Course			χ^2 = 7.7	0.006
Episodic	56%	27%		
Chronic	44%	73%		
Rapid-cycling	32%	56%	χ^2 = 5.7	0.02
GAF: mean (SD)	67.2 (17.9)	57.8 (15.4)	U = 1701	0.01
Disability (for BD)	30%	81%	χ^2 = 26.9	< 0.001
Antipsychotic treatment	57%	72%	χ^2 = 1.9	0.16
BMI: mean (SD)	28.8 (6.3)	33.7 (6.0)	U = 2895	< 0.001
Hypertension	12%	35%	χ^2 = 8.9	0.003

BD = bipolar disorder; BMI = body mass index; DM = diabetes mellitus; GAF = Global Assessment of Functioning; NOS = not otherwise specified; U = Mann–Whitney U test

Discussion

The prevalence of DM in our sample is similar to the rates reported in other studies; namely, those of Lilliker and Cassidy and others (6,7). Further, we found that BD patients with and without comorbid DM differed in their basic clinical characteristics. The main differences emerged in the clinical course of BD (that is, chronic vs episodic, as well as rapid cycling) and in disability rates, GAF score, BMI, and hypertension.

Given the growing interest in new-onset DM with respect to drug treatment—in particular, to treatment with antipsychotic drugs (11–13)—one would expect treatment with neuroleptics to be among the principal causes of the increased frequency of DM in BD patients. However, we were not able to find a significant association between DM and antipsychotic treatment. Yet, our analysis showed a trend toward higher use of antipsychotics in the group with comorbid DM. These results are consistent with those of Regenold and others (8). These authors investigated the prevalence of DM in psychiatric patients with BD I, schizoaffective disorder, major depression, schizophrenia, and dementia. They did not find any significant relation between antipsychotic use and DM in their sample.

Our sample of 26 subjects with DM was too small to assess whether there is a relation between different types of prophylactic treatment and DM frequency. This is an interesting question in view of the fact that lithium has been shown to posses insulin-like effects in human, animal, and in in vitro studies (1,2,14–16).

The finding of a more complicated course of BD in patients with DM is compatible with the view that DM and BD share alterations in several areas—such as dysregulation of the HPA axis or on the signal transduction level. However, discussion of possible links between BD and DM is beyond the scope of this article, and we can only briefly outline this issue. To give an example, disturbances in glycogen synthase kinase 3ß (GSK3ß) signalling play a role in insulin resistance—one of the processes involved in the etiology of DM type 2. GSK3ß is also one of the targets for lithium action. It is possible that additional disturbances in these mechanisms owing to a diabetic condition may accentuate the already-present alterations in BD, which will eventually be reflected in the clinical outcome. In other words, a diabetic condition seems to modify the course of BD. The same may be true with respect to the increased risk of DM in BD subjects. 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.

This study is limited by the difference in age between subjects with comorbid DM and those without. This difference could partly explain the higher rates of hypertension and BMI in the DM group, which was older. The results of logistic regression are compatible with this explanation: after correction for the effect of age, the association between hypertension and DM was not as marked as in the pairwise analysis. Another limitation is the cross-sectional study design. This means that the observed associations should be viewed as such and not necessarily interpreted as causal relations.

In summary, BD patients with comorbid DM appear to suffer from a more severe course of BD in terms of chronicity, rapid cycling, and overall functioning. These patients are also at a higher risk for high blood pressure and obesity. In addition, the results suggest that antipsychotic treatment, previously reported to be associated with an increased risk of DM, is not the major determinant for the higher rates of DM in BD patients; rather, other mechanisms could be responsible for this phenomenon. These findings urge further research in this area, because BD patients with comorbid DM have significantly poorer quality of life and contribute significantly to the socioeconomic burden of BD.

Funding and Support

This study was supported by grants from the Department of Psychiatry, Dalhousie University, and the Capital District Health Authority, and by an Elli Lilly Canada fellowship to Dr Ruzickova.

References

1. Van der Velde CD, Gordon MW. Manic-depressive illness, diabetes mellitus, and lithium carbonate. Arch Gen Psychiatry 1969;21:478–85.
2. Vendsborg PB. Lithium treatment and glucose tolerance in manic-melancholic patients. Acta Psychiatr Scand 1979;59:306–16.
3. Vestergaard P, Schou M. Does long-term lithium treatment induce diabetes mellitus? Neuropsychobiology 1987;17:130–2.
4. Heninger GR, Mueller PS. Carbohydrate metabolism in mania before and after lithium carbonate treatment. Arch Gen Psychiatry 1970;23:310–9.
5. Mueller PS, Heninger GR, McDonald RK. Insulin tolerance test in depression. Arch Gen Psychiatry 1969;21:587–94.
6. Lilliker SL. Prevalence of diabetes in a manic-depressive population. Compr Psychiatry 1980;21:270–5.
7. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156:1417–20.
8. Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with BD I affective and schizoaffective disorders independent of psychotropic drug use. J Affect Disord 2002;70:19–26.
9. Lustman PJ, Griffith LS, Clouse RE, Cryer PE. Psychiatric illness in diabetes mellitus. Relationship to symptoms and glucose control. J Nerv Ment Dis 1986;174:736–42.
10. American Psychiatric Association. Diagnostic and statistical manual for mental disorders. 4th ed. Washington (DC): APA; 1994.
11. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, and others. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–81.
12. Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. J Clin Psychiatry 2002;63:920–30.
13. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001;11:25–32.
14. Mannisto P, Koivisto V. Antidiabetic effects of lithium. Lancet 1972;2:1031.
15. Rossetti L. Normalization of insulin sensitivity with lithium in diabetic rats. Diabetes 1989;38:648–52.
16. Orena SJ, Torchia AJ, Garofalo RS. Inhibition of glycogen-synthase kinase 3 stimulates glycogen synthase and glucose transport by distinct mechanisms in 3T3-L1 adipocytes. J Biol Chem 2000;275:15765–72.

Manuscript received May 2003, revised, and accepted June 2003.
[1]Clinical Research Fellow, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.
[2]Research Nurse, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.
[3]Research Nurse, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.
[4]Professor, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.
Address for correspondence: Dr M Ruzickova, Department of Psychiatry, Dalhousie University, 5909 Jubilee Road, Halifax, NS B3H 2E2
e-mail: mruzicko@dal.ca

Résumé :Caractéristiques cliniques du trouble bipolaire avec et sans diabète sucré comorbide

Objectif : Plusieurs études ont rendu compte d'une prévalence plus élevée du diabète sucré (DS) de type 2 chez les patients souffrant de trouble bipolaire (TB). Les liens possibles entre ces deux maladies incluent le traitement, le mode de vie, les changements de la transduction de signal et possiblement, un lien génétique. Pour étudier cette relation de plus près, nous avons cherché à savoir s'il y a des différences quelconques dans les caractéristiques cliniques des patients souffrant de TB, avec et sans DS.

Méthode : Nous avons comparé les données cliniques de 26 sujets diabétiques et de 196 sujets non diabétiques du Maritime Bipolar Registry, âgés de 15 à 82 ans, ayant reçu des diagnostics de TB I (n = 151), de TB II (n = 65), et de TB non spécifié (n = 6). Le registre contenait des données démographiques de base et des détails sur le cours clinique de la maladie bipolaire, son traitement, et la comorbidité physique. Dans une analyse subséquente, nous avons examiné les variables indiquant des différences entre les groupes, à l'aide de la régression logistique en utilisant le diabète comme variable des résultats.

Résultats : La prévalence du DS dans notre échantillon était de 11,7 % (n = 26). Les patients diabétiques étaient significativement plus âgés que les patients non diabétiques (P < 0,001), avaient des taux plus élevés de cycles rapides (P = 0,02) et un cours chronique de TB (P = 0,006), avaient des scores inférieurs à l'échelle d'évaluation globale du fonctionnement (P = 0,01), recevaient plus souvent des indemnités d'invalidité pour TB (P < 0,001), et avaient des indices de masse corporelle plus élevés (P < 0,001) ainsi qu'une fréquence accrue d'hypertension (P = 0,003). Les antécédents à vie de traitement aux antipsychotiques n'étaient pas significativement associés à un risque élevé de diabète (P = 0,16); cependant, les données indiquaient une tendance à une utilisation plus fréquente d'antipsychotiques chez les sujets diabétiques.

Conclusions : Nos résultats indiquent que le diagnostic de DS chez les patients souffrant de TB est utile pour leur pronostic et leurs résultats.