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Type 2 Diabetes Mellitus: A Potentially Modifiable Risk Factor for Neurochemical Brain Changes in Bipolar Disorders

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ABSTRACT

BACKGROUND: Neuroimaging changes in bipolar disorder (BD) may be secondary to the presence of certain clinical factors. Type 2 diabetes mellitus (T2DM) damages the brain and frequently co-occurs with BD. Studying patients with both T2DM and BD could help identify preventable risk factors for neuroimaging changes in BD.

METHODS: We used 1.5T magnetic resonance spectroscopy to measure prefrontal *N*-acetylaspartate (NAA), which is mainly localized in neurons, and total creatine (tCr), an energy metabolite, in 19 BD patients with insulin resistance/glucose intolerance (BD + IR/GI), 14 BD subjects with T2DM (BD + T2DM), 15 euglycemic BD participants, and 11 euglycemic, nonpsychiatric control.

RESULTS: The levels of NAA and tCr were lowest among BD + T2DM, intermediate in the BD + IR/GI, and highest among the euglycemic BD and control subjects ($F_{3,55} = 4.57$, $p = .006$; $F_{3,55} = 2.92$, $p = .04$, respectively). Even the BD + IR/GI subjects had lower NAA than the euglycemic participants ($t_{43} = 2.13$, $p = .04$). Total Cr was associated with NAA ($\beta = .52$, $t_{56} = 5.57$, $p = .000001$). Both NAA and tCr correlated with Global Assessment of Functioning scores ($r_{46} = .28$, $p = .05$; $r_{46} = .48$, $p = .0004$, respectively).

CONCLUSIONS: T2DM, but also prediabetes, may be risk factors for prefrontal neurochemical alterations in BD. These changes were associated with poor psychosocial functioning and could indicate impaired energy metabolism. The findings emphasize the importance of improving diabetes care in BD and suggest potential options for treatment of neuroimaging alterations.

Keywords: Bipolar disorder, Global assessment of functioning, *N*-acetylaspartate, Prefrontal cortex, Total creatine, Type 2 diabetes mellitus

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Neuroimaging changes have been repeatedly documented in bipolar disorder (BD) but are not found in all studies (1–4). This heterogeneity of findings suggests that brain alterations in BD may be secondary to the presence of certain clinical factors (5). Yet, the specific variables associated with brain abnormalities in BD remain unknown. One potential and understudied source of neuroimaging changes in BD is the comorbidity with medical conditions known to damage the brain.

Type 2 diabetes mellitus (T2DM) is a frequent medical complication in patients with BD who have up to three times increased risk of T2DM relative to the general population (6–10). This is of clinical significance, as BD complicated by T2DM is associated with greater morbidity (11–14), lower treatment response (8), and greater chronicity and disability (11). And yet, T2DM remains undertreated and insufficiently monitored among BD patients (15–19). This is particularly concerning, as the brain is one of the targets for diabetic end-organ damage (20).

Some of the negative effects of T2DM on the brain are mediated through macrovascular (ischemic stroke) or small vessel disease. However, T2DM is also associated with more subtle, yet more direct, neuronal impairment through withdrawal of trophic factors and inhibition of insulin-responsive gene expression (20,21). In addition, impaired energy metabolism with resulting oxidative stress, the hallmarks of T2DM (22,23), may be particularly damaging to neurons, which have limited energy storage and a limited capacity to counter oxidative damage (20–22,24,25). Consequently, it is not surprising that patients with T2DM show global (26,27), as well as localized (28–32) neuroanatomical changes. Magnetic resonance spectroscopy (MRS) studies in T2DM have most frequently reported lower levels of brain *N*-acetylaspartate (NAA) (33–36), which further decrease with poorer glycemic control or insulin resistance (37,38). Interestingly, lower cortical NAA levels are also found in BD (4). Yet, no studies have directly investigated whether some of the brain changes reported in BD are associated with comorbid T2DM. Studying patients with both T2DM and BD could help identify preventable risk factors for neuroimaging changes in BD and could provide insight into their pathophysiology and possible treatment.

Therefore, we systematically evaluated glucose and insulin levels and obtained brain MRS data from euglycemic BD participants; BD subjects with insulin resistance (IR), glucose

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intolerance (GI), or T2DM; and euglycemic, nonpsychiatric control subjects. We hypothesized that 1) impaired glucose metabolism in BD would be associated with lower brain NAA; and 2) the NAA changes would be related to impaired energy metabolism, the hallmark of T2DM, as indirectly measured by brain levels of creatine and phosphocreatine (termed total creatine [tCr]). We also explored whether the neurochemical changes would be associated with negative clinical outcomes.

METHODS AND MATERIALS

This was a cross-sectional study of BD subjects recruited from the Maritime Bipolar Registry (13) and control subjects recruited through advertisement. The study was approved by the Ethics Committee of Capital District Health Authority and all included subjects signed the informed consent.

Inclusion/Exclusion Criteria

The subjects with BD were required to 1) have the diagnosis of bipolar I or II disorder made by a psychiatrist; and 2) be at least 18 years of age. Patients were excluded if they had 1) the diagnosis of organic mood disorder; 2) mood disorder not otherwise specified; or 3) more than one lifetime course of electroconvulsive therapy or electroconvulsive therapy within the last 6 months. The neuropsychiatrically healthy, euglycemic subjects were excluded if they had 1) a personal history of psychiatric disorders; or 2) T2DM. Subjects from any group were excluded if they 1) met any magnetic resonance imaging (MRI) exclusion criteria; 2) suffered from substance abuse in the last 12 months; had a history of 3) neurodegenerative disorders; or 4) cerebrovascular disease/stroke, as we were interested in the more subtle T2DM-related neuronal changes.

Diagnostic Assessments

For the detailed description of the diagnostic assessment, please see Ruzickova *et al.* (13). Briefly, the diagnostic interviews were performed by pairs of clinicians, according to the Schedule for Affective Disorders and Schizophrenia, Lifetime version (39). We also used National Institute of Mental Health-Life Chart Methodology (40); assessed the current level of functioning using the Global Assessment of Functioning (GAF) scale (41); and checked for early adversity using the Childhood Experience of Care and Abuse Questionnaire (42). Diagnostic information was reviewed in a blinded fashion in consensus meetings of the research team, which included a minimum of two psychiatrists. Each control subject also underwent the Schedule for Affective Disorders and Schizophrenia, Lifetime version interview and was included if found to have no personal or family history of Axis I psychiatric disorders. In all subjects, we also measured body mass index (BMI) using the formula BMI = weight (kg)/height (meters)^2.

Diagnosis of IR and T2DM

All patients who did not have a pre-existing diagnosis of T2DM (with evidence of treatment) had fasting plasma glucose (FPG) and fasting serum insulin tests performed and analyzed in a single laboratory with the same assay to eliminate variability. If FPG was >7 mmol/L, the test was repeated on another day to confirm the diagnosis of T2DM. If the diagnosis of T2DM was equivocal (the repeated test was <7 mmol/L or the initial FPG was between 5.7 and 6.9 mmol/L), we performed a 2-hour 75 g oral glucose tolerance test. Glucose intolerance was defined by a FPG <7.0 mmol/L and a glucose level >7.8 and <11.1 mmol/L, measured 2 hours after ingestion of 75 g of glucose. The diagnosis of T2DM was made if the 2-hour glucose level was >11.1 mmol/L, irrespective of FPG. These are standard diagnostic procedures for T2DM (43). In patients who did not meet laboratory criteria for T2DM or GI, we estimated IR using the homeostatic model assessment-insulin resistance (HOMA-IR) equation: HOMA-IR = FPG (mmol/L) × fasting serum insulin (μU/mL)/22.5.

The HOMA-IR strongly correlates with estimates using the euglycemic clamp method (44,45) and is a well accepted measure of IR. We used a HOMA-IR >2.0 to define IR (46). The participants with IR and GI were combined into a single group (BD + IR/GI group) for the analyses. We performed neuroimaging in participants with impaired glucose metabolism (BD + IR/GI and BD + T2DM) who were matched to euglycemic BD subjects and nonpsychiatric euglycemic control subjects by age and sex.

MRI Methods

All magnetic resonance acquisitions were performed with a 1.5 Tesla General Electric Signa scanner (General Electric Medical Systems, Fairfield, Connecticut) and a standard quadrature head coil. After a localizer scan, a T1-weighted spoiled gradient recalled scan was prescribed (flip angle = 40°, echo time = 5 msec, repetition time = 25 msec, field of view = 24 cm × 18 cm, matrix = 256 × 160 pixels, number of excitations = 1, no interslice gap, 124 images, 1.5 mm thick), followed by one single volume (20 × 20 × 20 mm) proton magnetic resonance spectroscopy acquisition with a probe point resolved spectroscopy sequence and the whole gradient mode (echo time = 30 msec, repetition time = 2000 msec, 320 acquisitions, 2500 Hz spectral bandwidth, 2048 data points). We acquired unsuppressed water and water suppressed spectra from the same location. The unsuppressed water signal was used for eddy current compensation and for metabolite quantification.

Voxel Placement

The spectroscopic region of interest (ROI) was prescribed blind to subject status in the left prefrontal cortex (PFC) (Figure 1), using previously validated methods (47,48). The PFC is involved in cognitive and emotional processing in mood disorders (49–51) and is among the most investigated regions for MRS in BD (4). Changes in PFC may contribute to impaired functioning of patients with BD even during periods of euthymia (50,52). In addition, prefrontal NAA levels are sensitive to T2DM and variations in glucose levels (38).

Spectral Analysis

We quantified metabolite levels with a linear combination model of in vitro spectra (LCModel version 6.1; http://s-provencher.com/pages/lcmodel.shtml) using previously validated methods (53). The method employs a basis set of concentration-calibrated model spectra of individual metabolites including lipids and macromolecules, as listed in Figure 1.