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Bipolar Disorder and Diabetes Mellitus: Epidemiology, Etiology, and Treatment Implications

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Introduction. *Bipolar disorder (BD) is a highly prevalent and disabling condition with significant mortality risk from suicide and other unnatural causes. This ignominious description is alongside recent observations that the majority of excess deaths in BD are secondary to medical comorbidity. The medical burden in BD is associated with a clustering of risk factors (e.g., obesity, smoking, unhealthy dietary habits) and inadequate utilization of preventative and primary healthcare. Diabetes mellitus (DM) is also a prevalent multifactorial disease which imparts substantial illness burden. Preliminary investigations indicate that patients who suffer from BD with comorbid DM have a more severe course and outcome, lower quality of life, higher prevalence of medical comorbidity and higher cost of illness.*

Methods. *We conducted a MedLine search of all English-language articles 1966–2004 using the key words: bipolar disorder, major depressive disorder, diabetes mellitus, glucose metabolism, mortality, overweight, obesity, body mass index. The search was supplemented with manual review of relevant references. Priority was given to randomized controlled data, when unavailable; studies of sufficient sample size are presented.*

Results. *Subpopulations of BD patients should be considered at high risk for DM. The prevalence of DM in BD may be three times greater than in the general population.*

Conclusions. *Bipolar disorder populations may be an at-risk group for glucose metabolic abnormalities. Opportunistic screening and vigilance for clinical presentations suggestive of DM is encouraged.*

Keywords Bipolar disorder, diabetes mellitus, comorbidity, mortality, insulin

INTRODUCTION

As a group of disorders, bipolar disorders (BD) are prevalent, chronic, and of multifactorial etiology (1,2). The age of onset of these disorders is early in life, and they often pursue an unremitting and protracted course. Moreover, BD impart significant morbidity and are associated with an increase in all-cause mortality (3–7). Emerging data indicate that the majority of excess deaths in BD are secondary to highly comorbid medical conditions (e.g., cardiovascular and endocrine) (8).

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both (9). Like BD, DM is

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prevalent; 8% of the adult population have DM, with higher rates in older populations. Several racial and ethnic groups are at particularly high risk (e.g., African Americans, Hispanics, and Asians (10)). Diabetes mellitus is associated with substantial illness-related morbidity and mortality. Persons with DM are at risk for acute life-threatening consequences such as hyperglycemia associated with ketoacidosis and nonketotic hyperosmolar syndrome. Long-term medical complications of DM include blindness, cardiovascular disease, end-stage renal disease, nontraumatic limb amputation, cognitive impairment, psychiatric disease, peripheral and autonomic neuropathy (9,10).

The therapeutic objectives in BD are to reduce symptoms, restore function, reduce human capital costs and all-cause mortality. The standardized mortality ratio (SMR) attributable to natural causes in BD has been estimated to be up to two-fold greater than the general population (8). It is a viable and testable hypothesis that greater clinical attention to somatic health issues could reduce overall morbidity and excess deaths in BD populations (11).

The reported frequent co-occurrence of BD and DM, and recent observation of the presence of DM as an adverse prognosticator for BD patients, suggests that both of these common maladies may have overlapping pathogenesis. A vista for further research is to parse out subpopulations of BD who are comorbid with DM, and further determine if this population comprises a unique subtype of BD.

The extant scientific literature describing the cross-sectional and longitudinal epidemiological associations between BD and DM is reviewed, and a summary of putative common underlying mechanisms between these two disorders is presented. Recommendations for screening and evaluating BD patients with preexisting or high risk for DM are offered. The objective of this article is not to review the impact of psychotropic medications on glucose metabolism, which is covered elsewhere (12).

Epidemiology

The available data indicate that the prevalence of glucose handling disturbances in select psychiatric populations (mood and psychotic disorders) is several-fold greater than the age-adjusted general population estimate (13,14). Original reports, which first appeared in pre-DSM and pre-psychopharmacological eras (15) chronicled higher rates (vs. general population) of abnormal glucose handling, insulin resistance, glucose intolerance and syndromal DM among psychiatric probands and among first-degree relatives (16,17). These original investigations did not permit definitive conclusions regarding the hazard rate for DM in BD due to methodological insufficiencies (e.g., non-standardization of psychiatric and DM diagnoses, the inclusion of heterogeneous samples, failure to control for relevant demography).

Results from more recent and rigorous investigations do indicate, however, that both cross-sectional and longitudinal associations exist between schizophrenia/depression and DM. Moreover, it has been suggested that schizophrenia may be an independent risk factor for DM and that insulin resistance in depression may be a salient intermediary between mood disorders and Alzheimer's disease (14,18–25).

Bipolar Disorder and Glucose Metabolism: Clinical Studies

Several investigations have scrutinized the interface between BD and DM (Table 1).

Gildea et al. (26) were among the first to report on glucose-handling disturbances in manic-depressive psychoses. Patients were investigated with both intravenous and oral dextrose tolerance testing (IVDTT, ODTT). For the IVDTT, patients received 50 ml of a 50% solution of dextrose over a period of 5 minutes. In the ODTT, patients either drank or were given by a stomach tube, a 250 ml solution containing at least 50 g dextrose. Subjects weighing more than 50 kg, were given 1 g of dextrose per 1 kg of body weight. They were compared to normal subjects (n=60) who were not matched on relevant variables (e.g., sociodemographic, anthropometry, and family history). The authors noted intravenous dextrose tolerance curves that were non-significantly different than the normal control group. Five of their patients, however, did exhibit prolonged ODTT curves. Several of the patients exhibiting abnormal ODTT curves had received barbiturates the evening preceding the testing. The authors concluded that abnormal oral results could be attributable to delayed absorption of dextrose from the gastrointestinal tract and could not be accepted as prima facie evidence of an intrinsic disorder of carbohydrate metabolism.

Van der Velde and Gordon (27) conducted two separate studies. The first investigation evaluated hospitalized manic-depressive patients (n=42) and compared them to an equal number of inpatient schizophrenics, matched for age, and length of hospitalizations. Patients were evaluated at fasting, and at 30 minutes, 1, and 2 hours after drinking a 75 g of glucose drink. A glucose tolerance sum (GTS) > 600 mg/100 cc was considered to be an abnormal response. It was determined that 50% (16/32) of the manic-depressive patients who were over the age of 40 showed a hyperglycemic response. By contrast, 20% (6/32) of the schizophrenic patients exhibited a hyperglycemic response.

The second study by this group investigated hospitalized manic-depressive patients (n=17), receiving a variety of psychotropic agents. Similar to the first study, 53% (9/17) of the manic-depressive patients, all over age 40, showed a hyperglycemic response. The authors concluded that the abnormal results (which exceeded population norms) were independent of the polarity of the manic-depressive episode and noted primarily in patients over the age of 40; an age cohort hitherto established at greater risk when compared to younger persons in the general population.

Table 1 Clinical Investigations of Bipolar Disorder—Diabetes Mellitus Comorbidity

Author and year	Study design	Patients	Comments
Gildea et al., 1943 (26)	Oral and intravenous dextrose tolerance test	N = 30 Manic-Depressive (Pre DSM) N = 6 manic, N = 18 depressed, N = 6 agitated depression Patients mostly treated Age: 18–64	- 0/34 (0%) iv dextrose tolerance tests abnormal - 6/30 (20%) oral dextrose tolerance "retarded decline" in blood sugar - " (no) evidence of an intrinsic disorder of carbohydrate metabolism"
Van der Velde et al., 1969a) (27)	Oral glucose tolerance test	N = 42 Manic-Depressives ("mostly unmedicated") Age: 18 - 71 N = 42 Schizophrenic patients All patients > 40 years old	- 16/42 (38%) manic-depressive patients exhibit "hyperglycemic response" - 6/42 (14%) schizophrenic patients exhibit "hyperglycemic response"
Van der Velde et al., 1969b) (27)	Oral glucose tolerance test	N = 17 Manic-Depressives (lithium naïve) Age: 48 – 86	- 9/17 (53%) manic-depressive patients exhibited a "hyperglycemic response"
Lilliker, 1980a) (28)	Retrospective chart review	N = 203 Manic depressives (DSM-II) DM defined as patients who were given a clinical diagnosis based on fasting blood sugar or substantiated medical history Patients mostly treated	- 20/203 (10%) were diagnosed with DM - 4/79 males, 16/124 females (13%) - Patients older than 45 years old, prevalence of DM 18% women, 6% men - Patients older than 65 years, prevalence of DM 23% and 16%, for women and men respectively
Lilliker, 1980b) (28)	Retrospective chart review	N=4508 total number of individuals discharged between 1973–78 with diabetic diet recorded in dietary record Patients mostly treated Age: 18–79	- 16/129 (12.4%) manic-depressive on diabetic diet - 38/1134 (3.3%) schizophrenic - 121/4379 (2.8%) overall
Lustman et al., 1986 (29)	Cross-sectional evaluation	N=114 diabetic patients random recuitment evaluated with NIMH DIS (DSM-III) Mean Age – 40 +/- 15.1	- 81/114 (71%) had a lifetime history of one criteria-defined psychiatric illness - 3/114 (3%) diagnosed with manic-depression - 37/114 (33%) diagnosed with depression - significant difference in glycated hemoglobin was observed in patients with a recent psychiatric illness (10.8%) to those never psychiatrically ill (9.6%) - psychiatric patients reported more symptoms of poor metabolic control and more distress associated with the symptoms than did patients never psychiatrically ill
Cassidy et al., 1999 (30)	Retrospective chart review	N=345 BD patients (DSM-III-R) DM diagnosis based on clinical analysis of blood glucose. Patients mostly treated Age: 20–74	- 36/357 (10%) diagnosed with DM - Total number of psychiatric hospitalizations significantly greater in diabetic group than in the age-matched comparison (non-diabetic BD patients)
Newcomer et al., 1999 (31)	Oral glucose tolerance test: 15-, 45-, 75- min post ingestion blood sampling	Schizophrenia N=10, BD N=10, Healthy controls N=11 (DSM-III-R) Patients mostly treated Age: 35.1+/- 10.2	- Study designed to assess glucose-induced changes in memory performance - Plasma glucose higher in schizophrenia than BD and normal control - Higher insulin levels in both SZ and BD than normal controls
Regenold et al., 2002 (34)	Retrospective chart review	N=243 BD (DSM-IV) DM defined based on clinical diagnosis in chart, OR the prescription of insulin or oral hypoglycemics (upon discharge) Comparison with four other diagnostic groups Patients mostly treated Age = 50–74	- Rates of type II DM among the five groups were: schizoaffective 10/20 (50%), BD-I 14/53 (26%), major depression 12/65 (18%), dementia 6/34 (18%). Schizophrenia 9/71 (13%) - Diabetic patients had higher BMI, but not a significantly higher use of psychotropic medication - Compared to national norms, DM rates were significantly elevated in BD-I, and schizoaffective patients
Ruzickova et al., 2003 (35)	Retrospective analysis of the Maritime Bipolar Registry	BD-I N=151 BD-II N=65 BD NOS N=6 (DSM-IV) DM ascertained based on previous diagnosis and evidence of treatment Patients mostly treated Age = 15–72	- 26/222 (12%) had DM - BD with comorbid DM were older (53 +/- 9 vs. 43 +/- 12), chronically ill, rapid cycling, lower GAF score - BD with comorbid DM higher long-term disability, higher BMI (34 +/- 6 vs. 29 +/- 6), higher rate of hypertension
Kessing et al., 2004 (36)	Retrospective Danish national registry	BD n=6683 Major Depressive Disorder n=29,065 Osteoarthritis n=108,525	- Risk of readmission for DM not increased in patients with depression or mania/BD compared to osteoarthritis

Lilliker (28) conducted a chart review to evaluate the cross-sectional prevalence of DM in manic-depressives, and compare prevalence rates to other psychiatric populations. This was a heterogenous population of bipolar patients, and included the following DSM-II diagnoses: manic-depressive illness, manic type; manic-depressive illness, depressed type: manic-depressive illness, circular type; manic-depressive illness, circular type, manic; and manic-depressive illness, circular type, depressed. A total of 203 cases of manic depression were found, and from this, 20 cases were identified with comorbid DM. The age range of the group was 28–77 with a mean age of 58 years. The reported prevalence of DM (9.9%) was significantly higher than the prevalence rate extracted from the 1960–62 National Health Survey (overall estimate 2%).

In a second study from the same group, hospital dietary records were harvested and cross-referenced to co-occurring psychiatric disorders. It was determined that 12.4% (16/129) of patients with manic-depressive illness were on a diabetic diet. This was a significantly greater proportion than was found among patients with other psychiatric disorders [e.g., schizophrenia (3.3%; 38/1134), mental retardation (2.3%; 10/423)], or among the total number of individuals discharged from their hospital between 1973–78 (2.8%; 121/4379).

Lustman et al. (29) used the Diagnostic Interview Schedule (DIS) and DSM-III criteria to establish the lifetime prevalence of psychiatric diagnoses in patients undergoing annual DM evaluation. The subjects were evenly divided between type I and II DM. A history of at least one psychiatric disorder was identified in 81/114 (71%) patients undergoing evaluations. The diagnosis of major depressive episode (33%) and generalized anxiety disorder (41%) were the most commonly assigned diagnoses. Three of the subjects (2.6%) had a mania diagnosis, while one (0.9%) had a diagnosis of schizophrenia. Although the number of subjects in this study is small, the prevalence of BD in this sample is higher than general population estimates.

Cassidy et al. (30) evaluated hospitalized DSM-IIIR-defined BD (manic or mixed subtype; n=345) for a comorbid diagnosis of DM. The age range was 20–74, with a mean age of 40.6. The frequency of DM in this study group was determined and compared with the expected frequency calculated as a weighted average based on sex and age from national norms. The authors also reported variables characterizing the course and severity of psychiatric illness in BD subjects with DM, compared to a group of non-diabetic, age-matched subjects. The frequency of DM in BD was 9.9% versus 3.5% in the comparison study group ($p<0.001$). The age of first psychiatric hospitalization in the diabetic group did not differ from the matched group, however, the total number of hospitalizations in the diabetic group was significantly greater. The age of onset and duration of illness were not significantly different.

Newcomer et al. (31) evaluated the effects of circulating glucose levels on memory performance in DSM-IIIR-defined schizophrenia and two comparison groups; healthy controls, and subjects with BD. All subjects were tested after double-blind assignment with either 50 g anhydrous dextrose, plus 4 mg sodium saccharin, or with 23.7 mg saccharin alone, followed by cognitive testing on a complex battery. Subjects had baseline, 15-, 45-, and 75-minute post-injection blood sampling and cognitive testing. Subjects were matched for age, sex and body mass index (BMI). Within the BD group, six of the ten patients were receiving lithium carbonate (mean dose: 1450.0 +/– 350.7 mg per day), three were receiving carbamazepine, and two received SSRIs. Another six of ten patients with BD were receiving conventional antipsychotics.

A significant two-way interaction between diagnostic group and plasma sample time was detected for plasma glucose concentration ($p=0.04$), with a similar trend for insulin ($p=0.06$). Plasma glucose values were higher in the schizophrenics, as compared with the BD and normal subjects ($p=0.04$ and 0.001, respectively). Plasma insulin values also varied across the diagnostic groups, at the 75-min sampling time only ($p=0.01$), as a result of higher insulin values in subjects with BD and schizophrenia when compared with normal subjects ($p=0.006$ and 0.01, respectively). Plasma cortisol levels were also evaluated; there were no glucose-induced effects on plasma cortisol. Notably, cognitive performance, as measured by paragraph recall, was increased during the hyperglycemic treatment relative to the saccharin condition in patients with schizophrenia ($p = 0.009$) but this was not the case in patients with BD ($p = 0.75$) or in normal control subjects ($p = 0.85$).

Regenold et al. (32) tested the hypothesis that an increased polyol pathway flux was operative in patients with unipolar and bipolar mood disorders. Increased flux through the sorbitol or polyol pathway may be salient in the pathogenesis of diabetic neuropathy (33). Through the polyol pathway, glucose is converted to sorbitol by the enzyme aldose reductase using NADPH as a cofactor. The activity of this pathway is influenced by myriad variables, notably hyperglycemia, which increases the flux of glucose through this pathway. Patients (n=5 BD-I, n=5 BD-II, n=10 MDD) were compared to an age-, race-, and sex-matched control group (n=10). Cerebrospinal fluid (CSF) was obtained through lumbar puncture and analyzed for sorbitol concentration. Data from BD-I and BD-II was combined into a single group. The mean (+/– SD) sorbitol concentration was BD (22.9 +/– 4.6 umoles/L) > MDD (19.0 +/– umoles/L) > normal controls (15.6 +/– 1.9 umoles/L). One-way ANOVA of mean CSF concentrations showed a significant difference among the three diagnostic groups ($p=0.0002$). The polyol pathway is in delicate interplay with monoaminergic functioning, and as such, may be of relevance to the pathophysiology of mood disorders.

Regenold et al. (34) further aimed to clarify the intrinsic relationship between abnormal glucose metabolism and several psychiatric disorders, with a cross-sectional review. Controlling for demography, anthropometric and treatment variables, the authors reported that the prevalence of type II DM in schizoaffective disorder (50%) and BD-I (26%), were higher than national norms ($p<0.05$). Psychiatric diagnoses and BMI, and not psychotropic medication, were significant and independent predictors of DM diagnosis.

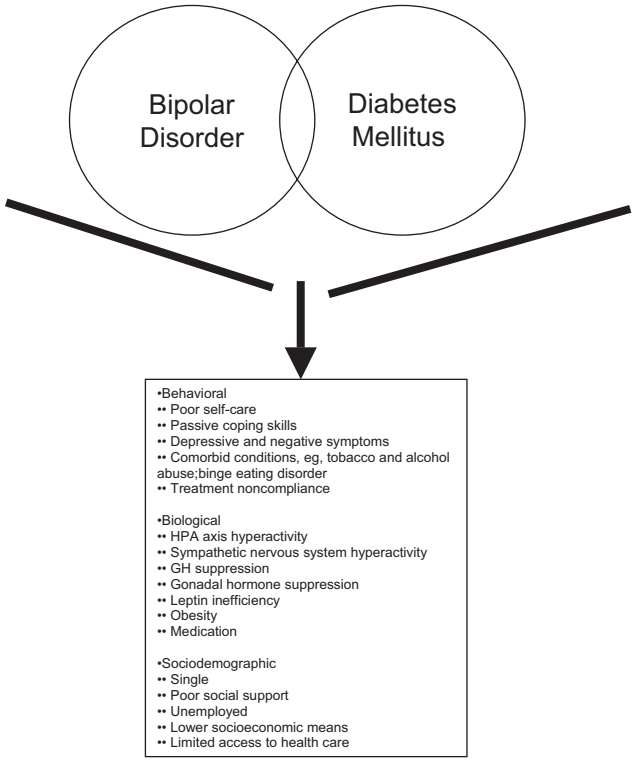
Ruzickova et al. (35) compared clinical data of 26 diabetic DSM-IV-defined BD and 196 non-diabetic subjects from a bipolar registry. Subjects were aged 15–82 years with a psychiatric diagnosis of BD-I (n=151), BD-II (n=65), and BD not otherwise specified (NOS) (n=6). The prevalence of DM in their sample was 11.7%. The two groups were similar in respect to the sex distribution, but probands with DM were significantly older (mean age = 52.5 +/– 9.6) than subjects without DM (mean age 42.8 +/– 12.3). When compared with non-diabetic subjects, subjects with comorbid DM had a more chronic course (p=0.006), more rapid cycling (p=0.02), and lower scores on the Global Assessment of Function scale (p=0.01). In addition, 81% of individuals with comorbid DM were on long-term disability, compared to 30% of probands without DM (p<0.01). Subjects with comorbid DM had a higher mean BMI and prevalence of hypertension. Consistent with the finding of Regenold et al. (34), a stepwise logistic regression analysis identified age and BMI, but not psychotropic medications, as independent variables associated with a diagnosis of DM.

Kessing et al. (36) employed survival analysis to compare the risk of DM for patients hospitalized for depression (n=29,035) or BD (n=6,683) to a group of patients (n=108,525) with a diagnosis of osteoarthritis in a nationwide Danish registry. Previously, this group had identified an increased risk of developing dementia or Parkinson's disease in patients with depression or mania, compared to patients with osteoarthritis (37,38). Overall the risk of readmission for DM was not increased for patients who were previously admitted for depression or BD compared to patients with osteoarthritis. Based on these findings, the authors suggest that the risk of DM in depressive or BD patients is not greater than that in patients with other chronic medical illness. We note, however, that methodologically relying on hospital readmission as a proxy for DM may have underestimated the prevalence of DM conditions. Moreover, the use of osteoarthritics as a control group in this investigation may not have been ideal, as the biological association between osteoarthritis and insulin resistance has not been carefully parsed out (39–41).

Taken together, available investigations scrutinizing the interface between BD and glucose metabolism provide results which suggest that subpopulations of BD patients may manifest clinical (or sub-clinical) glucose handling disturbances. Moreover, the comorbid presence of DM may be an adverse prognosticator for individuals with BD. Definite conclusions however, await results from more rigorous and standardized studies in the area.

Bipolar Disorder and Glucose Metabolism: Etiology and Pathophysiology

Diabetes mellitus type II is multifactorial in etiology, with a substantial genetic component. Multiple explanations for the increased comorbidity between BD and DM may be operative (Figure 1).



Adapted from Keck et al. (12)

Figure 1 Bipolar disorder and diabetes mellitus: Comorbidity or subphenotype?

The symptomatic structure of BD is predominantly depressive symptoms of varying severity. Atypical depressive symptoms (e.g., fatigue, hyperphagia) could possibly mediate sedentary inactive lifestyle and excess carbohydrate ingestion in BD. It has been previously reported that being overweight and the categorical prevalence of obesity in addition to abnormal eating patterns (e.g., bulimia nervosa, binge eating disorder) — all identified risk factors for DM, are more prevalent in BD than in the general population. Fat-patterning studies indicate that a greater proportion of adiposity in BD subjects is viscerally distributed (42,43).

Disturbances in circadian rhythms are an antecedent, prodrome and component of bipolar episodes. Abnormalities in the functioning of the suprachiasmatic nucleus (SCN) of the hypothalamus may presage sleep-wake cycle disturbances in BD and concurrent glucose homeostatic dysregulation (44,45). The SCN is a major coordinator of internal circadian organization and is itself synchronized with the day:night cycle by direct neural input from specialized retinal photoreceptors (46,47). The SCN may be relevant to comorbid disturbances in both the sleep-wake cycle and glucose handling (44) in bipolar populations. For example, preclinical studies have demonstrated that electrical stimulation of the SCN is associated with hyperglycemia, increases in liver glycogen phosphorylase activity, and

decrease in liver glycogen content (48). It is further noted that SCN-lesioned rats exhibit higher plasma insulin levels than sham-operated rats (44).

High rates of micro and macrovascular disease are recognized in subjects with DM (49,50). White matter lesions, detectable as hyperintensities in T2-weighted magnetic resonance imaging (MRI) scans, are considered to be an indicator of cerebrovascular complications in DM (51,52). It is noteworthy that a number of studies have also found white matter hyperintensities to be associated with BD (53–55), though it is not yet established whether these lesions presage psychopathology.

A large body of evidence from epidemiological, case control and cohort studies documents an unequivocal causal link between cigarette smoking and health risks. Individuals with BD have significantly higher rates of smoking than the general population (56). Individuals with DM have a heightened risk of morbidity and premature death associated with the development of microvascular complications among smokers. Smoking is also related to the premature development of microvascular complications of DM and may have a role in the development of type II DM.

The current and lifetime prevalence of alcohol and substance abuse and dependence in BD populations is higher than in the general population. Pancreatitis from alcohol and/or other toxins can result in disturbances of the exocrine pancreas contributing to DM risk. Persons with BD frequently receive multiple pharmacological treatments that are associated with clinically significant weight gain and disruption of the glucose homeostatic system. (See Keck et al. (12) for a comprehensive review.)

Psychological stress is accompanied by release of counterregulatory hormones (i.e., glucocorticoids, growth hormone, catecholamines, glucagon) which raise blood levels of glucose through lipolysis, proteolysis, gluconeogenesis, and glycogenolysis (10). It has been suggested that persistent stress (allostatic load) may eventually lead to increased insulin resistance as a consequence of increased release of these counterregulatory hormones (10). Hitherto, the operating characteristics of stress response systems have largely been scrutinized in cohorts with major depression, with a paucity of data in BD. Notwithstanding, similar aberrant stress responses have been noted in various phases of BD, on the basis of pharmacological tests of hypothalamic-pituitary-adrenal axis reactivity (57–59).

Immune system activation—particularly inflammatory cytokine activity—has been implicated as an underlying factor in depression. Inflammatory cytokines (IL-1, IL-6 and TNF-α) mediate a syndrome of "sickness behavior," the features of which (e.g., appetite and sleep disturbances, fatigue) resemble symptoms typically seen in depression (60). Consistent with this, a number of studies have detected increased inflammatory cytokine production in patients with major depression (61). Though these cytokines have not been extensively studied in BD, other indicators of inflammatory activity, such as increased levels of C-reactive protein (62), IL-1 receptor antagonist (63), soluble IL-6 receptor (64), and evidence of T-lymphocyte activation (64–67) have been detected in BD patients. In recent years, it has become apparent that inflammatory cytokines likely play a pathogenic role in type II DM, both by promoting insulin resistance and by contributing to the destruction of pancreatic β cells (68–71). Considerable evidence implicates adipose tissue as a major source of diabetogenic cytokines (68,72,73), and age-related increases in cytokine production by monocytes and macrophages might also play a role (74–76). The possibility of inflammatory cytokine activity as a link between DM and BD remains to be investigated.

Decreased glucose utilization in the brain has been associated with depressive disorders (10,77). Glucose utilization, which can be quantified using positron emission tomography (PET) (77), is dependent on transporter-mediated glucose uptake. Several isoforms of facilitative glucose transporters have been identified, at least four of which can be found in the brain. The expression of these transporters may be regulated, to varying extents, by glucose and/or insulin (78–80). There is evidence that deficient functioning of insulin-sensitive glucose transporters may be a cause of insulin resistance in type II DM (81–83). Thus, abnormal structure and/or function of glucose transporters is an unstudied possible disturbance in mood disorder populations with DM.

Abnormalities in intracellular signaling are hypothesized to be relevant to BD pathophysiology. Glycogen synthase kinase-3 (GSK-3) is a protein kinase highly involved in a broad range of biological processes (e.g., cell growth, gene transcription). Insulin inhibits a GSK-3-mediated signaling pathway that modulates the stimulation of glycogen and protein synthesis. In addition, GSK-3 phosphorylates and regulates the functions of many other metabolic signaling and structural proteins (see Gould et al. (84) and Cohrn et al. (85) for comprehensive reviews). GSK-3 inhibitors are under development for the treatment of neurodegenerative diseases, stroke, cancer, chronic inflammatory diseases, type II DM and BD. Lithium and valproic acid appear to be inhibitors of GSK-3, suggesting that GSK-3 dysregulation may be relevant to the pathophysiology of both BD and DM (85,86).

Abnormalities in phospholipid metabolism and impaired fatty acid-related signal transduction processes have been described in both mood disorders and DM (for review, see Horrobin and Bennett (87)). Interestingly, psychotropic agents, such as lithium and certain anticonvulsants, have been reported to modulate brain phospholipid metabolism (88). Characterizing the interface between BD and DM may be usefully informed by elucidating the pathophysiological relevance of phospholipid and fatty acid metabolism in both disorders.

The etiologies of BD and DM each include a substantial genetic component. While rare monogenic forms may exist, BD and DM are, for the most part, complex polygenic disorders in which multiple genes, as well as environmental factors, play a role (89–91). Although the vast majority of genetic studies of BD and DM, to date, have focused on the two disorders individually, at least two genetic loci have been considered as candidates for involvement in both disorders. For example, Chiba et al. (92) have reported evidence for association of

insulin resistance and depression to a polymorphism in the tyrosine hydroxylase gene, which is closely linked to the insulin gene. Notably, some (but not all) studies have provided evidence for the involvement of this locus in susceptibility to BD (90,91). Another gene considered to be a potential common susceptibility factor for BD and DM is the Wolfram syndrome gene (WFS1). Wolfram syndrome is a rare monogenic syndrome caused by loss-of-function mutations in WFS1 (93). The clinical spectrum of Wolfram syndrome includes DM (89), and this syndrome is often associated with psychiatric illness (94). These observations have prompted investigators to search for other, less deleterious variants of WFS1 that might influence susceptibility to both DM and psychiatric disorders, including BD, in the general population (93,95). These efforts have led to the identification of a number of WFS1 gene variants, however evidence for association of any particular variant with both DM and BD has not yet been found.

Both BD and DM are diseases heterogenous in pathophysiology and etiology. Several genetic, molecular, cellular, physiological, and behavioral variables common to both disorders may explain the frequent of co-occurrence of both conditions.

Bipolar Disorder and Diabetes Mellitus: Clinical Implications

A comprehensive evaluation of patients with BD should include an assessment of medical and behavioral factors associated with obesity and DM. All patients should be screened for exercise habits, eating patterns, comorbid binge eating disorder, bulimia nervosa, caffeine dependence, smoking and thyroid dysfunction. Furthermore, patients should have baseline weight and BMI measured; although waist-to-hip ratio is an optional measure, it is a reliable proxy of visceral adipose tissue. Baseline blood work should include a screen for DM, which includes measures of fasting blood glucose and lipid fractionation (Tables 2 and 3).

The metabolic syndrome has been described as the simultaneous presence of truncal obesity, dyslipidemia, disturbed insulin and glucose metabolism, and hypertension. Not all persons manifest the full spectrum of this syndrome, with subsyndromal variants frequently encountered. The metabolic syndrome is a risk factor for type II DM and coronary artery disease; it is apparent that patients with BD (and schizophrenia) cluster several dimensions of this syndrome. Clinicians should routinely screen for this syndrome in all patients with BD, at the time of diagnosis, and periodically with ongoing care (96,97).

The diagnosis and treatment of BD patients with DM should include care from a multidisciplinary coordinated team. In patients with pre-DM (impaired fasting glucose/impaired glucose tolerance) lifestyle modification is strongly recommended (Table 3) (98).

Gestational diabetes mellitus (GDM) complicates approximately 4% of all pregnancies in the United States. The puerperium is an at risk period for affective instability in BD populations (99,100). It is not known if mood disorder during pregnancy is

Table 2 Criteria for the Diagnosis of DM

Normoglycemia	IFG or IGT	Diabetes
FPG <100 mg/dl 2-h PG <140 mg/dl	FPG ≥100 and <126 mg/dl (IFG) 2-h PG ≥ 140 and <200 mg/dl (IGT)	FPG ≥ 126 mg/dl 2-h PG ≥ 200 mg/dl Symptoms of diabetes and casual plasma glucose concentration ≥200 mg/dl

From ADA Position Statement 2004 (98)

Table 3 Criteria for Testing for DM in Asymptomatic Adult Individuals

1. Testing for diabetes should be considered in all individuals at age 45 years and above, particularly in those with a BMI 25 kg/m^{2*}, and, if normal, should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI 25 kg/m^{2*}) and have additional risk factors:

- are habitually physically inactive
- have a first-degree relative with diabetes
- are members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- have delivered a baby weighing >9 lb or have been diagnosed with GDM
- are hypertensive (140/90 mmHg)
- have an HDL cholesterol level 35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250 mg/dl (2.82 mmol/l)
- have PCOS
- on previous testing, had IGT or IFG
- have other clinical conditions associated with insulin resistance (e.g., PCOS or acanthosis nigricans)
- have a history of vascular disease

* May not be correct for all ethnic groups. PCOS, polycystic ovary syndrome.
From ADA Position Statement 2004 (98)

an additional vulnerability factor for GDM. The mental health care professional should be familiar with the American Diabetes Association (ADA) Position Statement in these high-risk individuals (98).

The ADA guidelines on the treatment of DM recommend that high risk patients be screened earlier and monitored more frequently (98). The basic principles of managing DM in BD are not dissimilar from non-psychiatrically affected diabetic patients. Unique, however, to this patient population, is their vulnerability to depression (which may be associated with poor DM care compliance), propensity for impulsivity and suicidal behavior, comorbidity with alcohol and substance use disorders, higher prevalence of cardiovascular disease and smoking, frequent overeating and inactivity, and exposure to weight-gain promoting psychotropic agents.

CONCLUSION

Bipolar disorder and DM are prevalent, disabling, and highly co-occurring diseases. Extant data do not permit definitive conclusions regarding the hazard rate of DM in BD populations. Taken together, a testable hypothesis is that DM is more prevalent in some subpopulations of BD. Future investigations should attempt to elucidate the hazard risk in well-characterized, newly-diagnosed BD populations. It would be further interesting to parse out shared pathophysiology between the two disorders. There is tremendous need for treatment studies which could inform practitioners on the safe and effective therapeutic avenues to implement in patients comorbid with BD and DM. In the interim, practitioners should familiarize themselves with the ADA physician statement on screening and treating DM (9,98).

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