A Longitudinal Study of the Relationships Between Mood Symptoms, Body Mass Index, and Serum Adipokines in Bipolar Disorder

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ABSTRACT

Objective: There is a bidirectional relationship between obesity and mood disorders, with each increasing the risk of developing the other. This relationship suggests that they have overlapping pathophysiologic mechanisms. Adipose tissue–derived hormones, or adipokines, regulate appetite and metabolism and have activity in limbic brain regions, making them potential shared etiologic factors between elevated body mass index (BMI) and mood disorders. However, the precise relationships between BMI, mood, and adipokines are unknown.

Methods: We measured the serum levels of adiponectin, lipocalin-2, resistin, adipsin, and leptin in 53 people with early-stage *DSM-IV*–defined bipolar disorder, diagnosed with the Mini-International Neuropsychiatric Interview, and 22 healthy comparison subjects. Participants were followed at the University of British Columbia Mood Disorders Centre between June 2004 and June 2012. We were primarily interested in determining, in patients, (1) whether BMI and recent mood episodes predicted adipokine levels and (2) whether adipokine levels in turn predicted subsequent mood relapses and change in BMI.

Results: Using linear regression, we found that (1) past-6-month mood episodes predicted lower adiponectin ($\beta = -0.385$, $P = .04$) and adipsin ($\beta = -0.376$, $P = .03$) levels and higher lipocalin-2 levels ($\beta = 0.411$, $P = .03$), (2) BMI did not predict adipokine levels, and (3) treatment with second-generation antipsychotics was associated with higher resistin levels ($\beta = 0.482$, $P < .01$). Furthermore, lower adiponectin ($\beta = -0.353$, $P = .01$) and leptin ($\beta = -0.332$, $P = .02$) levels predicted depressive relapse over 12 months, while higher adipsin ($\beta = 0.496$, $P < .01$) and leptin ($\beta = 0.421$, $P < .01$) levels predicted BMI gain.

Conclusions: Our results suggest that mood episodes and medication treatment contribute to adipokine abnormalities in bipolar disorder and that adipokines influence psychiatric illness course and BMI change. Adipokines may represent a novel pathophysiologic mechanism linking elevated BMI and mood disorders and deserve further study as potential mood-regulating molecules.

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There is a complex, bidirectional relationship between mood disorders and obesity. Major depressive disorder and bipolar disorder predispose affected individuals to gaining weight, becoming obese, and developing metabolic complications such as diabetes.[1,2] These observations predate the availability of obesogenic psychotropic medications,[3] suggesting that a propensity for weight gain is inherent to mood disorders. The reverse relationship also holds, in that being overweight (body mass index [BMI] = 25–29.9) increases the probability of developing a depressive illness by 25% while being obese (BMI ≥ 30) increases it by more than 50%.[1] Moreover, obese patients with mood disorders have less favorable psychiatric outcomes than normal-weight patients, including shorter euthymic intervals, more frequent relapses, lower medication response rates, and greater inter-episode cognitive impairment.[4–7]

The most parsimonious explanation for this reciprocal association is that obesity and mood disorders have overlapping pathophysiologic mechanisms. Alterations in serum adipokine levels are potentially one such mechanism. Adipokines are a diverse group of peptide hormones produced primarily or exclusively by adipose tissue.[8,9] They play key roles in controlling appetite and food intake and in regulating metabolic processes such as glucose and fatty acid utilization.[10–12] Their rate of synthesis covaries with adipose tissue mass, and obesity-related increases in leptin, resistin, lipocalin-2, and adipsin, and decreases in adiponectin, are implicated in the pathophysiology of metabolic disorders such as diabetes.[10,11,13,14] Adipokine levels are also altered in mood disorders,[15,16] and several of them have activity in limbic brain regions,[17,18] influence mood-regulating neurotransmitters such as dopamine,[19] and modulate depressive behaviors in preclinical models.[20,21] Thus, there are theoretical grounds to suspect that adipokines are shared etiologic factors between mood disorders and increased BMI.

If adipokines are indeed shared etiologic factors, they should influence, and be influenced by, both mood symptoms and BMI. However, no longitudinal studies have examined the relationships between mood, BMI, and adipokines in patients with mood disorders. We therefore conducted the current analysis to investigate (1) whether current BMI and past-6-month mood episodes predicted

Clinical Points

- The factors underlying the bidirectional association between obesity and mood disorders are poorly understood.
- In early-stage bipolar disorder patients, recent mood episodes predicted altered adipokine levels, and adipokine levels in turn predicted subsequent depressive relapse and gain in body mass index.
- Adipokines deserve study as potential novel therapeutic targets in people with mood disorders.

the serum levels of 5 adipokines—adiponectin, lipocalin-2, resistin, adipsin, and leptin—in bipolar disorder patients and (2) whether adipokine levels in turn predicted prospectively ascertained BMI change and mood relapses over 12 months. Since mood stabilizers and second-generation antipsychotics (SGAs) influence the outcomes of interest, including adipokine levels,[22] we controlled our analyses for them. For comparison purposes, we also examined the relationship between BMI and adipokines in healthy subjects who did not have bipolar disorder. We predicted that mood episodes and BMI would be associated with alterations in adipokine levels in patients and that adipokine levels would predict relapse into depression and hypomania or mania (hypo/mania) and BMI gain.

METHODS

Subjects

Serum samples were obtained between June 2004 and June 2012 from bipolar disorder patients and healthy subjects enrolled in the Systematic Treatment Optimization Program for Early Mania (STOP-EM), a prospective study of early-stage bipolar disorder. A detailed description of STOP-EM was published previously.[23] Briefly, patients aged 14–35 years who experienced their first manic or mixed episode ≤ 3 months before assessment were recruited from the University of British Columbia (UBC) Mood Disorders Centre and affiliated sites. Patients with or without comorbid psychiatric and substance use disorders were enrolled, so long as their primary diagnosis was bipolar disorder. Healthy subjects aged 14–35 years were recruited from the Vancouver area through print advertisements and online forums such as Craigslist. The UBC Clinical Research Ethics Board approved the protocol, and written informed consent was obtained prior to any study procedures' taking place.

Clinical Assessments

Diagnoses of bipolar disorder and first manic/mixed episode, based on *DSM-IV* criteria, were confirmed with the Mini-International Neuropsychiatric Interview (MINI).[24] Healthy subjects were administered the MINI and enrolled if they had no personal or family history in first- or second-degree relatives of psychiatric illness. Sociodemographic and clinical data were collected using a standardized protocol. Mood and psychotic symptoms were quantified in patients with the Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), and Brief Psychiatric Rating Scale (BPRS). Participants were weighed in a nonfasting state in light clothing with footwear removed, and their BMI (weight [kg]/height [m]^2) was calculated. Underweight was defined as BMI < 18.50, normal weight as BMI = 18.50–24.99, overweight as BMI = 25.00–29.99, and obesity as BMI ≥ 30.00.

Patients received treatment according to clinical practice guidelines from the Canadian Network for Mood and Anxiety Treatments.[25] Patients and healthy subjects were reassessed at 6 monthly intervals. At these visits, their weights were recorded and, in patients, clinical rating scales were repeated and medication treatments were noted. Episode recurrence and the number of days ill were determined by clinician assessment, patient-completed National Institute of Mental Health Life Charts, and collateral information from health records as needed.

Collection and Analysis of Serum Samples

A single nonfasting blood sample was acquired from each participant, either at enrollment or at a 6-monthly follow-up visit, and typically in the early afternoon. In all participants, blood samples were obtained within 4 years of the first manic episode (or within 4 years of enrollment for healthy subjects). Twenty milliliters of blood was collected by venipuncture into 2 Becton, Dickinson and Company (Rutherford, New Jersey) 367820 Vacutainer serum tubes. These were centrifuged at 3,000 rpm for 10 minutes to separate the serum, which was aliquotted into Eppendorf tubes and stored at −80°C. Adipokine levels were measured with the Human Adipokine Magnetic Bead Panel I kit (HADK1MAG-61 K, Millipore—adiponectin, lipocalin-2, resistin, adipsin; EMD Millipore) or Human Metabolic Hormone Magnetic Bead Panel (HMHMAG-34 K, Millipore—leptin; EMD Millipore). Twenty-five microliters of serum was added to sample wells and incubated with antibody-immobilized beads overnight at 4°C. The samples were then washed and incubated with detection antibodies (60 minutes, room temperature), followed by addition of streptavidin-phycoerythrin (30 minutes, room temperature). Plates were read on MAGPIX using xPONENT software (Luminex Corporation). Adipokine levels were calculated using standard curves.

Data Analysis and Statistics

Statistical analyses were carried out using IBM SPSS Statistics for Windows 22.0 (SPSS Inc). Comparisons were 2-tailed, with a significance level of $\alpha = .05$. Sociodemographic characteristics were compared between patients and healthy subjects using independent-sample t test, χ^2 test, or Fisher exact test as appropriate.

For our primary analyses, the time point at which adipokine levels were measured was considered "time-zero" (T_0) for each participant. The primary analyses were designed to determine (1) whether mood episodes in the preceding 6 months (T_{-6mo}) and T_0 BMI predicted T_0 adipokine levels and (2) whether T_0 adipokine levels predicted prospectively

Table 1. Regression Models Employed in Primary and Secondary Analyses[a]

Model	Dependent Variable(s)	Predictors
Models in patients		
Predictors of adipokine levels	T_0 serum levels of: • Adiponectin • Lipocalin-2 • Resistin • Adipsin • Leptin	• T_0 BMI • T_{-6mo} mood episode (Y/N) • Treatment with mood stabilizer (Y/N) • Treatment with SGA (CPZE) • Age • Gender
Predictors of depressive relapse[b]	T_{+12mo} days with depression	• T_0 serum levels of adiponectin, lipocalin-2, resistin, adipsin, leptin • T_0 BMI • T_0 YMRS and MADRS scores • T_{-6mo} days with depression • T_{-6mo} days with hypo/mania • Treatment with mood stabilizer (Y/N) • Treatment with SGA (CPZE) • Mood illness duration (mo)
Predictors of hypo/manic relapse[b]	T_{+12mo} days with hypo/mania	• T_0 serum levels of adiponectin, lipocalin-2, resistin, adipsin, leptin • T_0 BMI • T_0 YMRS and MADRS scores • T_{-6mo} days with depression • T_{-6mo} days with hypo/mania • Treatment with mood stabilizer (Y/N) • Treatment with SGA (CPZE) • Mood illness duration (mo)
Predictors of change in BMI[b]	T_{+12mo} BMI change	• T_0 serum levels of adiponectin, lipocalin-2, resistin, adipsin, leptin • T_0 BMI • T_0 YMRS and MADRS scores • T_{-6mo} days with depression • T_{-6mo} days with hypo/mania • Treatment with lithium (Y/N) or divalproex (Y/N) • Treatment with risperidone (CPZE), olanzapine (CPZE), or quetiapine (CPZE) • Mood illness duration (mo)
Models in healthy subjects		
Predictors of adipokine levels	T_0 serum levels of: • Adiponectin • Lipocalin-2 • Resistin • Adipsin • Leptin	• T_0 BMI • Age • Gender
Models comparing patients and healthy subjects		
Predictors of adipokine levels	T_0 serum levels of: • Adiponectin • Lipocalin-2 • Resistin • Adipsin • Leptin	• Diagnosis (patient vs healthy subject) • T_0 BMI • Diagnosis × T_0 BMI interaction • Age • Gender

[a]All models were constructed using multiple linear regression.
[b]These models were created iteratively. All predictors were entered into the first iteration. In the second iteration, predictors included those that were significantly associated with the dependent variable in the first model ($P < .1$) to a maximum of 5 for mood relapses and 4 for BMI change. Predictors entered in the second iteration are shown in Tables 5 and 6.
Abbreviations: BMI = body mass index, CPZE = chlorpromazine equivalents, hypo/mania = hypomania or mania, hypo/manic = hypomanic or manic, MADRS = Montgomery-Asberg Depression Rating Scale, SGA = second-generation antipsychotic, T_0 = at the time of adipokine measurement, T_{-6mo} = in the 6 months prior to adipokine measurement, T_{+12mo} = in the 12 months after adipokine measurement, YMRS = Young Mania Rating Scale.

ascertained BMI change and mood relapses over 12 months (T_{+12mo}). The statistical models employed for these analyses are described in the following text and are summarized in Table 1.

To investigate the impact of BMI and recent mood episodes on adipokine levels while minimizing multiple comparisons, we constructed a single multivariate multiple regression model with all 5 adipokines as the dependent variables. Predictors included BMI at the time of adipokine measurement, presence or absence of a mood episode in the preceding 6 months, self-reported treatment with mood stabilizers (Y/N) and SGAs (in total chlorpromazine equivalents [CPZE]) at the time of adipokine measurement, age, and gender. A significant result for BMI and/or mood episodes was followed up with univariate models examining the impact of the same predictors on each individual adipokine. If the multivariate model was significant for mood episodes, the follow-up models entered past-6-month depressive and hypo/manic episodes (Y/N) separately.

To investigate whether adipokine levels predicted subsequent time with depression and hypo/mania, and BMI change, we constructed 3 linear regression models. The dependent variables were (1) the number of days with depression in the 12 months after adipokine measurement, (2) the number of days with hypo/mania over 12 months, and (3) BMI change over 12 months. To keep the number

Table 2. Sociodemographic Characteristics of Patients (N = 53) and Healthy Subjects (N = 22) at the Time of Adipokine Measurement

Variable	Bipolar Disorder Patients (N = 53) Mean (SD)	Healthy Subjects (N = 22) Mean (SD)	*P*
BMI	25.1 (3.8)	22.9 (2.7)	.02
Age, y	23.1 (4.6)	25.0 (5.2)	.12
Years of education	14.0 (2.3)	15.1 (3.0)	.11
	% (n)	% (n)	
BMI category			.08
Normal-weight	50.9 (27)	77.3 (17)	
Overweight	41.5 (22)	22.7 (5)	
Obese	7.5 (4)	0 (0)	
Gender			.73
Male	45.3 (24)	40.9 (9)	
Female	54.7 (29)	59.1 (13)	
Ethnicity[a]			.66
White	73.6 (39)	76.2 (16)	
Asian	15.1 (8)	19.0 (4)	
Other	11.3 (6)	4.8 (1)	

[a]n = 74; 1 value missing in healthy subjects.
Abbreviation: BMI = body mass index.

Table 3. Clinical Characteristics of Patients

Characteristic	Mean (SD)
Rating scale score	
YMRS[a]	2.3 (5.3)
MADRS[a]	4.8 (6.8)
BPRS	20.8 (4.0)
Total number of mood episodes	
Depression[a]	1.4 (1.8)
Hypo/mania[a]	1.7 (1.4)
Duration of mood disorder (including prior depressions and hypomanias), mo	38.2 (49.6)
Time since first mania, mo	10.8 (12.2)
	% (n)
Mood state[a]	
Euthymic (MADRS < 12 and YMRS < 12)	80.8 (42)
Subsyndromal depression (MADRS 12–19)	11.5 (6)
Depressed (MADRS ≥ 20)	3.8 (2)
Hypomanic (YMRS 12–19)	0 (0)
Manic (YMRS ≥ 20)	3.8 (2)
Pharmacotherapy	
Mood stabilizer	84.9 (45)
Second-generation antipsychotic	58.5 (31)
Mood stabilizer + antipsychotic	54.7 (29)
Antidepressant	11.3 (6)
No medication	11.3 (6)
Lifetime substance dependence	
Alcohol[a]	5.8 (3)
Marijuana[b]	7.8 (4)
Other drugs[a]	7.7 (4)

[a]n = 52; 1 value missing.
[b]n = 51; 2 values missing.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, hypo/mania = hypomania or mania, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

of predictors in line with our sample size, we created these models iteratively. In the first step, predictors for mood relapses included serum levels of the 5 adipokines, BMI at adipokine measurement, YMRS and MADRS scores at adipokine measurement, the number of past-6-month days with depression and hypo/mania, treatment with mood stabilizers (Y/N) and SGAs (total CPZE), and mood illness duration. Predictors for BMI change were the same, except each of the mood stabilizers and SGAs was entered separately, given their different propensities for causing weight gain. In the second step, we retained predictors that were associated with the dependent variables ($P < .1$) in the first model, up to a maximum of 5 for mood relapses and 4 for BMI change (as we had data from fewer patients for this outcome).

We also conducted exploratory analyses to investigate whether the association of BMI with adipokines differed between patients and healthy subjects. To determine whether higher BMI at the time of adipokine measurement predicted adipokines in healthy subjects, we constructed a multivariate multiple regression model with all 5 adipokines as the dependent variables and T_0 BMI, age, and gender as predictors. It was followed up by univariate models examining the impact of these predictors on each individual adipokine. To directly compare the association between BMI and adipokines in patients and healthy subjects, we constructed a multivariate multiple regression model including both patients and healthy subjects, with the 5 adipokines as the dependent variables and diagnosis (patient vs healthy control), T_0 BMI, a diagnosis × T_0 BMI interaction term, age, and gender as predictors. It was followed up with univariate models for each individual adipokine.

RESULTS

We obtained serum samples from 53 patients and 22 healthy subjects who were included in our analyses assessing predictors of adipokine levels. Forty-three patients had data for depressive and hypo/manic relapses, and 37 had data for BMI change; these data were included in analyses examining the association of adipokines with these outcomes. Participants' sociodemographic characteristics are outlined in Table 2, and patients' clinical characteristics are listed in Table 3.

Association of Recent Mood Episodes and Current BMI With Adipokines in Patients

Eighty-one percent of patients (n = 42) were euthymic at the time of adipokine measurement, 12% (n = 6) had subsyndromal depression, and 7% (n = 4) were depressed or manic (Table 3). Fifty-seven percent (n = 30) had experienced a mood episode in the previous 6 months: 8% (n = 4) depression only, 34% (n = 18) hypo/mania only, and 15% (n = 8) both. Their mean time symptomatic was 66.3 (45.8) days. Patients' mean (SD) BMI at adipokine measurement was 25.1 (3.8). Fifty-one percent (n = 27) were normal-weight, 42% (n = 22) were overweight, and 8% (n = 4) were obese.

Multivariate regression demonstrated that past-6-month mood episodes ($F_5 = 2.878$, $P = .03$) and SGA treatment ($F_5 = 3.354$, $P = .01$) predicted adipokine levels in aggregate. BMI was not associated with adipokine levels. The follow-up univariate models showed that past-6-month hypo/mania predicted lower adiponectin ($\beta = -0.385$, $t = -2.083$, $P = .04$) and higher lipocalin-2 ($\beta = 0.411$, $t = 2.185$, $P = .03$), while past-6-month depression predicted lower adipsin ($\beta = -0.376$, $t = -2.302$, $P = .03$) (Table 4). SGA treatment was associated

Table 4. Multiple Regression Analysis Showing Predictors of Serum Adipokine Levels in Patients[a]

	Adiponectin			Lipocalin-2			Resistin			Adipsin			Leptin		
Predictor	β	*t*	*P*	β	*t*	*P*	β	*t*	*P*	β	*t*	*P*	β	*t*	*P*
BMI	−0.172	−1.006	.32	0.101	0.581	.56	−0.009	−0.056	.96	0.044	0.255	.80	−0.124	−0.715	.48
Past-6-month hypo/mania	**−0.385**	**−2.083**	**.04**	**0.411**	**2.185**	**.03**	0.186	1.112	.27	0.066	0.360	.72	−0.043	−0.224	.82
Past-6-month depression	0.004	0.026	.98	−0.168	−1.017	.31	0.059	0.402	.69	**−0.376**	**−2.302**	**.03**	0.054	0.325	.75
Mood stabilizer use (Y/N)	−0.124	−0.820	.42	−0.039	−0.257	.80	−0.037	−0.272	.79	−0.070	−0.470	.64	0.175	1.070	.29
SGA use (CPZE)	0.237	1.469	.15	−0.179	−1.092	.28	**0.482**	**3.285**	**.002**	−0.243	−1.507	.14	−0.190	−1.118	.27
Age, y	0.198	1.299	.20	−0.186	−1.196	.24	0.159	1.148	.26	−0.071	−0.463	.65	0.071	0.428	.67
Gender	−0.001	−0.003	1.00	−0.081	−0.474	.64	−0.180	−1.186	.24	−0.146	−0.873	.39	−0.287	−1.572	.12

[a]Significant results ($P < .05$) are highlighted in boldface.
Abbreviations: BMI = body mass index, CPZE = chlorpromazine equivalents, hypo/mania = hypomania or mania, SGA = second-generation antipsychotic.

with higher resistin (β = 0.482, $t = 3.285$, $P < .01$). BMI was not associated with adipokine levels in the univariate models (all $P \geq .32$).

Association of Adipokines With Subsequent Time in Mood Episodes and BMI Change in Patients

Forty-two percent of patients (18/43) experienced a mood episode in the 12 months following adipokine measurement: 23% (n = 10) depression, 7% (n = 3) hypo/mania, and 12% (n = 5) both. Their mean time symptomatic was 106.8 (72.7) days. The mean change in BMI over 12 months was modest at −0.1 (2.2), but was highly variable (range, −4.5 to 6.1).

In the first iteration of the regression model investigating time depressed, significant predictors included adiponectin, adipsin, leptin, BMI, and past-6-month days with depression. In the second iteration, lower adiponectin (β = −0.353, $t = -2.594$, $P = .01$), lower leptin (β = −0.332, $t = -2.504$, $P = .02$) and more past-6-month days depressed (β = 0.537, $t = 3.840$, $P < .01$) remained predictors (Table 5). In the first iteration of the model investigating time hypo/manic, predictors included adiponectin, BMI, past-6-month days depressed, past-6-month days hypo/manic, and YMRS score. In the second iteration, a nonsignificant trend suggested that higher adiponectin predicted time hypo/manic (β = 0.284, $t = 1.785$, $P = .07$) (Table 5). However, this model failed diagnostic tests (residuals were not normally distributed), and we cannot be confident in the results. In the first iteration of the model investigating BMI change, predictors included adiponectin, adipsin, leptin, and YMRS score. In the second iteration, higher adipsin (β = 0.496, $t = 3.039$, $P < .01$), higher leptin (β = 0.421, $t = 2.831$, $P < .01$), and higher YMRS score (β = 0.449, $t = 2.887$. $P < .01$) remained predictors (Table 6).

BMI and Adipokines in Healthy Subjects

Healthy subjects' mean (SD) BMI at adipokine measurement was 22.9 (2.7). Seventy-seven percent (n = 17) were normal-weight, 23% (n = 5) were overweight, and none were obese. Multivariate regression demonstrated that BMI did not predict adipokine levels in aggregate ($F_5 = 1.155$, $P = .39$), and the univariate models showed that it did not predict individual adipokine levels (all $P > .33$). The multivariate regression model including patients and healthy subjects showed no main effect of BMI ($F_5 = 0.211$, $P = .96$) or diagnosis ($F_5 = 0.864$, $P = .51$) on adipokines in aggregate and no BMI × diagnosis interaction ($F_5 = 0.877$, $P = .50$). Thus, there was no association between BMI and adipokines across patients and healthy subjects, adipokine levels did not differ between patients and healthy subjects, and the impact of BMI on adpokines also did not differ based on diagnosis. The same was true for individual adipokines in the univariate regressions (diagnosis: all $P > .58$; BMI: all $P > .45$; BMI × diagnosis interaction: all $P > .62$).

Table 5. Regression Analyses Showing Predictors of Time With Depression and Hypomania and/or Mania[a,b]

	Time With Depression			Time With Hypo/Mania		
Predictor	β	*t*	*P*	β	*t*	*P*
Adiponectin	**−0.353**	**−2.594**	**.01**	0.284	1.875	.07
Lipocalin-2						
Resistin						
Adipsin	−0.238	−1.708	.10			
Leptin	**−0.332**	**−2.504**	**.02**			
BMI	−0.202	−1.542	.13	0.220	1.306	.20
Mood stabilizer use (Y/N)						
SGA use (CPZE)						
Past-6-month days with depression	**0.537**	**3.840**	**.001**	0.146	.908	.37
Past-6-month days with hypo/mania				0.216	1.312	.20
YMRS score				0.167	1.059	.30
MADRS score						
Total mood illness duration						

[a]A blank cell in the table indicates that the predictor was not significantly associated with the dependent variable in the first model. Predictors were determined using linear regression. To keep the number of predictors in line with our sample size, we iteratively created 2 regression models for each dependent variable (days with depression and days with hypo/mania). In the first model, predictors included all of those listed in the first column of the table. In the second, we retained those predictors that were associated with the dependent variable ($P < .1$) in the first model, to a maximum of 5. β values and *P* values show the association of predictors with the dependent variables in the second model.
[b]Significant results ($P < .05$) are highlighted in boldface.
Abbreviations: BMI = body mass index, CPZE = chlorpromazine equivalents, hypo/mania = hypomania or mania, MADRS = Montgomery-Asberg Depression Rating Scale, SGA = second-generation antipsychotic, YMRS = Young Mania Rating Scale.

DISCUSSION

This was the first study to prospectively examine mood symptoms, BMI, and adipokines in mood disorder patients.

Table 6. Regression Analyses Showing Predictors of Change in BMI in the 12 Months After Adipokine Measurement[a,b]

	Change in BMI		
Predictor	β	*t* Value	*P* Value
Adiponectin	0.303	1.903	.07
Lipocalin-2			
Resistin			
Adipsin	**0.496**	**3.039**	**.005**
Leptin	**0.421**	**2.831**	**.009**
BMI			
Treatment with lithium			
Treatment with valproate			
Treatment with risperidone			
Treatment with olanzapine			
Treatment with quetiapine			
Past-6-month days with depression			
Past-6-month days with hypo/mania			
YMRS score	**0.449**	**2.887**	**.007**
MADRS score			

[a]A blank cell in the table indicates the predictor was not significantly associated with the dependent variable in the first model. Predictors were determined using linear regression. To keep the number of predictors in line with our sample size, we iteratively created 2 regression models for the dependent variable (BMI change). In the first model, predictors included all of those listed in the first column of the table. In the second, we retained those predictors that were associated with the dependent variable ($P < .1$) in the first model, to a maximum of 4. β values and *P* values show the association of predictors with the dependent variable in the second model.

[b]Significant results ($P < .05$) are highlighted in boldface.

Abbreviations: BMI = body mass index, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

In keeping with the hypothesis that adipokines are shared etiologic factors between mood disorders and elevated BMI, we found that recent mood episodes predicted the serum levels of several adipokines in early-stage bipolar disorder, while a number of adipokines predicted subsequent time depressed and BMI gain. We also found a relationship between treatment factors, particularly SGAs, and adipokines. Our results suggest that adipokines may represent a novel pathophysiologic mechanism linking obesity and mood disorders and deserve further study as potential mood-regulating molecules.

A somewhat unexpected negative finding was the lack of association between BMI and adipokines in both patients and healthy subjects. This finding is most likely due to the weight distribution of our sample: half of patients and over three quarters of healthy subjects were normal-weight, and only 8% and 0%, respectively, were obese. While the link between obesity and altered adipokine levels is well known, it is not known whether higher BMIs in the normal-weight or overweight ranges are associated with adipokine alterations. In any case, the low obesity rate in our sample probably led us to underestimate the impact of BMI on adipokines, which would almost certainly have been greater in subjects with higher obesity rates.

The adipokines we measured play key roles in controlling food intake and metabolic processes. Leptin has satiety effects via receptors in the mediobasal hypothalamus,[26] but chronically elevated leptin leads to leptin resistance and a loss of satiety.[27,28] Adiponectin increases insulin sensitivity and enhances pancreatic β-cell survival through antiapoptotic and proliferative effects,[29] while adipsin is an insulin secretagogue.[11] Resistin, when present at low levels, also enhances β-cell survival, but at higher levels it contributes to insulin resistance by down-regulating insulin receptors and decreasing β-cell mass.[14,30] Data for lipocalin-2 are conflicting, with one study suggesting that it contributes to insulin resistance, but a second indicating that it protects against it.[31,32]

Our results thus highlight pathways through which mood symptoms and treatment factors could have negative metabolic consequences in bipolar disorder. The adipokine changes associated with recent mood episodes—lower adiponectin, lower adipsin, and, possibly, higher lipocalin-2—would be expected to contribute to insulin resistance. This is also true of the higher resistin seen with SGA treatment. These are potentially important findings in light of the fact that, although bipolar disorder patients are approximately 70% more likely to be obese than people without bipolar disorder,[33] they are 200%–300% more likely to develop diabetes.[34–36]

Our findings that leptin and adipsin were positively associated with 12-month BMI change also shed light on mechanisms underlying weight gain in bipolar disorder. Higher leptin has in fact been associated with weight gain in most longitudinal studies in nonpsychiatric samples,[37] a result that is generally interpreted as a sign of emerging leptin resistance in people with higher levels. Downstream effects of adipsin include triglyceride accumulation in adipose tissue via fatty acid esterification and inhibition of lipolysis,[38] suggesting pathways by which it could contribute to increased BMI.

Leptin and adiponectin, the two adipokines negatively associated with depressive relapse, have activity in brain reward circuits important to bipolar disorder.[39] In preclinical models, they have receptors in the prefrontal cortex, hippocampus, and amygdala and exhibit neuroprotective effects.[18,40–44] Leptin regulates the firing of ventral tegmental area dopaminergic neurons that synapse onto the ventral striatum,[19] and in human functional magnetic resonance imaging studies,[17,45] low serum leptin was associated with reduced activity in the nucleus accumbens and other reward-processing areas. Low serum adiponectin is associated with increased hippocampal excitotoxicity and, in humans, with reduced hippocampal volume.[18,46] In rodents, genetic knock-out of leptin and adiponectin lead to increased behavioral despair, while knocking out leptin receptors eliminates antidepressant responses to fluoxetine and desipramine.[47] Conversely, administering leptin and adiponectin in animals with functioning receptors has antidepressant effects.[20,21]

However, the roles of leptin and adiponectin in mood disorders have not been well characterized. Most studies were cross-sectional, with some reporting low serum levels of these molecules in depression,[48,49] while others found no relationship or higher levels.[50–52] For leptin, the picture is clouded by obesity-related leptin resistance, which is mediated by decreased leptin transport across the blood-brain barrier and the down-regulation of brain leptin

receptor signaling.[26] Thus, in normal-weight individuals, lower serum leptin leads to reduced central nervous system penetration and signaling, while in obese individuals, higher leptin has the same effects. In keeping with a primary antidepressant effect for leptin, lower central nervous system leptin has been consistently demonstrated in depressed patients and suicide attempters,[53,54] and several studies[55–57] report that the relationship between higher serum leptin and depression is seen only in obese individuals. For adiponectin, a recent meta-analysis[15] determined that lower levels were significantly associated with depression when it was measured using radioimmunoassay, a sensitive technique, but not with enzyme-linked immunosorbent assay (ELISA), which is less sensitive, and that the relationship between low adiponectin and depression was further obscured by the presence of more females, who generally have greater adiponectin levels than males, in the depressed groups.

Our study must be viewed in light of its limitations. Its naturalistic design limits our ability to establish causal relationships between BMI, mood symptoms, and adipokines. We did not collect fasting blood samples, although adipokine levels can differ in the fasting and postprandial states,[58] adding a confounding variable to our analyses. We did not correct our exploratory analyses for multiple comparisons. Our patients were in the early stages of bipolar disorder, were largely euthymic, and had low rates of obesity. Further work will be needed to determine if our findings hold true in patients with longer illnesses, in acute mood episodes, and with higher obesity rates. Almost all of our patients received pharmacotherapy for bipolar disorder, introducing the confounding effect of medication use. However, including treated patients made our findings generalizable to routine clinical practice, and we controlled for medication use in our analyses. Finally, we did not gather data on diet and exercise, variables that might have independent effects on adipokine levels.

Nonetheless, this is the first longitudinal study to demonstrate that mood episodes predict adipokine levels in mood disorder patients and that adipokines predict subsequent psychiatric illness course and BMI gain. They make a persuasive case for investigating the impact of adipokines in other psychiatric illnesses with high obesity rates and mood components, such as major depressive disorder, personality disorders, and psychotic illnesses.

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