A Prospective Observational Study of Obesity, Body Composition, and Insulin Resistance in 18 Women With Bipolar Disorder and 17 Matched Control Subjects

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Objective: Patients with bipolar disorder are at increased risk for diabetes and cardiovascular diseases, possibly because of more severe insulin resistance. The primary purpose of this study was to determine whether insulin resistance is characteristic of bipolar disorder.

Method: The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was performed in 18 women with DSM-IV bipolar I disorder, and results were compared to those of 17 matched controls. Other risk factors were compared, including blood pressure, blood lipids, and abdominal obesity by computed tomography (CT). Additionally, substrate utilization was measured by indirect calorimetry, and free-living energy expenditure was estimated using wearable activity monitors. All data were collected between February 2006 and December 2007.

Results: Patients with bipolar disorder were no more insulin resistant than controls after accounting for generalized obesity (mean ± SEM HOMA-IR = 2.7 ± 0.7 vs. 2.5 ± 0.7, for patients and controls, respectively; p = .79). Although blood lipid profiles were generally similar in patients and controls, obese patients had higher blood pressure than controls. Obese patients had more mean ± SEM total abdominal fat (718.1 ± 35.1 cm^2 vs. 607.4 ± 33.6 cm^2; p = .04), and tended (p = .06) to have more visceral abdominal fat. Patients oxidized 13% less fat during resting conditions, although their resting metabolic rate was similar to that of controls.

Conclusion: Women with bipolar I disorder were no more insulin resistant than matched controls after accounting for their level of obesity. However, they were more hypertensive, had higher amounts of abdominal obesity, and had reduced rates of fat oxidation. Therefore, women with bipolar I disorder may be at a heightened risk for future weight gain and concomitant risk for diabetes and cardiovascular disease.

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The alarming increase in obesity in the United States[1] and around the world[2–6] is a paramount public health concern affecting children, middle-aged and older men, and women across a variety of ethnic and racial groups. Recent studies suggest that patients with bipolar disorder have been particularly afflicted by the rampant increase in obesity. Indeed, these patients have a higher prevalence of obesity,[7–12] diabetes,[13–16] dyslipidemia,[17,18] hypertension,[7] and cardiovascular disease[7,19] than the general population. The etiology of obesity in patients with bipolar disorder likely involves a combination of genetic, lifestyle, and medication influences.

Regardless of the etiology, insulin resistance in obesity has been shown to be a common thread among metabolic disorders,[20] as well as cardiovascular disease,[21,22] and is strongly associated with type 2 diabetes.[23] In addition to generalized obesity by either body fat or body mass index (BMI) criteria, individuals with greater amount of central adiposity or abdominal fat[24] develop insulin resistance and its corresponding sequelae more frequently than those with peripheral body fat distribution.[25] Evidence

also suggests that an impaired capacity for fat oxidation leads to greater weight gain[26] and is associated with insulin resistance in obesity and type 2 diabetes.[27] Thus, the metabolic disturbances of insulin resistance and type 2 diabetes appear to include dysregulated fat metabolism as well as impaired glucose metabolism.

While the etiology of these associated metabolic disorders in bipolar patients is certainly complex, it is not known whether these patients are more insulin resistant than would be expected for their level of generalized obesity. Moreover, it is not known whether patients with bipolar disorder can be characterized by the subclinical correlates of insulin resistance, including abdominal fat accumulation or an impaired capacity for fat oxidation.

Insulin resistance is thought to be a unifying feature of diabetes, hypertension, dyslipidemia, and cardiovascular disease. Therefore, identifying and treating insulin resistance has immense preventative potential. The overall goal of this study was to determine whether insulin resistance, as well as subclinical features of insulin resistance, i.e., body fat distribution, energy expenditure, and lower postabsorptive fat oxidation, distinguishes bipolar I patients from healthy controls. Our primary aim was to compare insulin resistance in women with bipolar I disorder to race-, age-, and BMI-matched controls. Our second aim compared body fat distribution (abdominal and skeletal muscle–associated adipose tissue) in women with bipolar I disorder to controls. Lastly, in an attempt to explain potential differences that may be observed in obesity and/or insulin resistance between controls and bipolar patients, we compared components of energy balance (energy expenditure and dietary intake).

METHOD

The University of Pittsburgh's Institutional Review Committee approved the study, and all subjects provided written, informed consent at the time of their initial visit to the Clinical and Translational Research Centers (CTRC). All data were collected between February 2006 and December 2007. Due to the known effects of gender on body composition and regional fat distribution (men typically have much higher amounts of visceral abdominal adipose tissue), we decided to study only women. Participants were excluded if taking chronic medications known to adversely affect glucose homeostasis (thiazide diuretics, oral glucocorticoids, nicotinic acid, and oral steroids) or had a history of myocardial infarction, peripheral vascular disease, neuromuscular disease, proteinuria, liver disease, current alcohol or substance abuse, or current malignancy. Women who were pregnant or lactating or who had lost or gained > 5 kg in the past month were also excluded.

Standing height and weight were determined to the nearest centimeter and gram, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters to characterize women who were of normal weight (BMI < 25) or obese (BMI > 29.9). Participants were classified as either premenopausal or postmenopausal. Postmenopausal status was defined as not having had a menstrual period for at least 12 months.

Subjects

Bipolar patients (N = 18). Patients with DSM-IV Bipolar I disorder were recruited from the Bipolar Disorders Center for Pennsylvanians (BDCP); all patients were euthymic at study entry and were treated with ≤ 3 medications. Bipolar patients qualified as euthymic if they had a Clinical Global Impressions rating score below 3 that was maintained for 8 consecutive weeks.

Patients were excluded if they had ever received olanzapine and/or clozapine treatment, due to the well-documented effect of these medications on glucose homeostasis.[28] Patients taking medications known to affect weight (e.g., valproic acid and lithium) were not excluded, as this restriction would have severely hampered participant recruitment. Patient history of medication was obtained through BDCP medical records and self-report at time of consent.

Matched controls (N = 17). Matched controls were defined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P)[29] as having no lifetime history of mood, anxiety, psychotic, eating, sleeping, or somatoform disorder, nor could they ever have been treated with any psychotropic medication. Control subjects were matched to bipolar patients by race/ethnicity, age, and BMI.

Screening procedures. All subjects were admitted to the CTRC after an overnight fast and completed informed consent, the SCID-I/P, a food frequency questionnaire[30] (FFQ), and a blood draw to measure full lipid panel (cholesterol [CHOL], low-density lipoprotein [LDL], very–low-density lipoprotein [VLDL], high-density lipoprotein [HDL], and triglycerides), glucose, and insulin levels. Insulin resistance was defined by the homeostatic model assessment of insulin resistance (HOMA-IR; Glucose (mmol/L) × Insulin (μU/mL)/22.5).[31] This model correlated well with estimates using the euglycemic clamp method (r = 0.88).[32]

Insulin resistance, blood glucose, and lipids. Fasting levels of insulin were measured using the radioimmunoassay procedure developed by Pharmacia (Pharmacia Biotech, Uppsala, Sweden). Serum triglycerides and blood lipids were measured using an enzymatic method (Wako Diagnostics, Richmond, Va.). Plasma glucose was measured by means of an automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, Ohio).

Blood pressure. A conventional mercury sphygmomanometer was used for the measurement of blood

pressure. Prior to measurement, the participant rested quietly in a seated position with the back supported and feet flat on the ground. Systolic and diastolic blood pressures were defined as the average of 2 measures.

Experimental Procedures

Body composition. Body composition (i.e., total body fat, fat mass [FM] and fat-free mass [FFM]) were assessed using dual-energy x-ray absorptiometry (DXA; model DPX-L; Lunar Corp., Madison, Wis.). Abdominal subcutaneous (SUB), visceral (VISC), and intermuscular adipose tissue (IMAT) were assessed using computed tomography (CT) as previously described.[24] Briefly, a cross-sectional area of abdominal fat was assessed with a single CT scan centered upon the L4–L5 vertebral disk space. A single slice between the anterior superior iliac crest and the inferior margin of the patella divided by 2 was used for the intermuscular adipose assessments.

Energy expenditure. Resting metabolic rate and substrate (fat and carbohydrate) oxidation were assessed using systemic indirect calorimetry with an open canopy system (DeltaTrac, Anaheim, Calif.) after an overnight fast. All subjects were asked to refrain from activity the day of testing, i.e., take elevator instead of stairs. Prior to testing, calibration of both pressure and gas were completed. Subjects were instructed to rest comfortably and quietly for at least 10 minutes while they were provided with an explanation of procedures. The plastic canopy was placed over the subjects head and neck with the vinyl skirt covering and tucked under the torso. Participants were also instructed to refrain from fidgeting and sudden movements throughout the test. Resting metabolic rate was assessed over a period of 35 minutes although the first 5 minutes of data were discarded, since they have been shown not to reflect resting metabolic rate.[33] Data were obtained at 30-second intervals. The equation developed by K. N. Frayn, Ph.D.,[34] was used to determine rates of substrate oxidation in $g \times minutes^{-1}$.

Total free-living energy expenditure and active energy expenditure were estimated using a SenseWear Pro Armband (BodyMedia, Inc., Pittsburgh, Pa.). The SenseWear Pro Armband was worn for a period of 5 days. Participants were instructed not to take the armband off except for bathing. A unit of metabolic equivalent (MET) is defined as the number of calories consumed per minute in an activity relative to the basal metabolic rate. One MET is the caloric consumption while at complete rest, whereas the SenseWear Pro Armband divides activity into 3 categories: (1) sedentary (≤ 3.0 METs), (2) moderate (3.0–6.0 METs), and (3) vigorous (6.0–9.0 METs). The armband is a multi-sensor device consisting of a body-contoured monitor with adjustable straps to keep the sensor in contact with the arm during a variety of activities and conditions. The armband has been shown to be a valid determinant of free-living energy expenditure.[35] Data retrieved from the armband were analyzed via customized algorithms to determine derived energy expenditure and level of activity. Data were accepted into analyses if participants wore the armband no less than 80% of the 24-hour period.

Energy intake. To determine potential difference in energy intake and macronutrient composition, a food frequency questionnaire (FFQ)[30] was completed by subjects. This FFQ has been shown to provide a reasonable estimate of energy intake and macronutrient composition.[36]

Statistical Analyses

Statistical analyses were performed using SPSS software version 13.0 (SPSS Inc., Chicago, Ill.). All data are expressed as mean ± SEM. Differences in primary aims and secondary aims were conducted using 2-way analyses of variance (ANOVAs) to determine main effects (factor 1 = weight, and factor 2 = diagnosis) and interaction effects between obese patients and obese controls and normal weight patients and normal weight controls. Pearson correlation coefficient was used to determine the relationship between insulin resistance, percentage body fat, VISC fat, and energy expenditure.

RESULTS

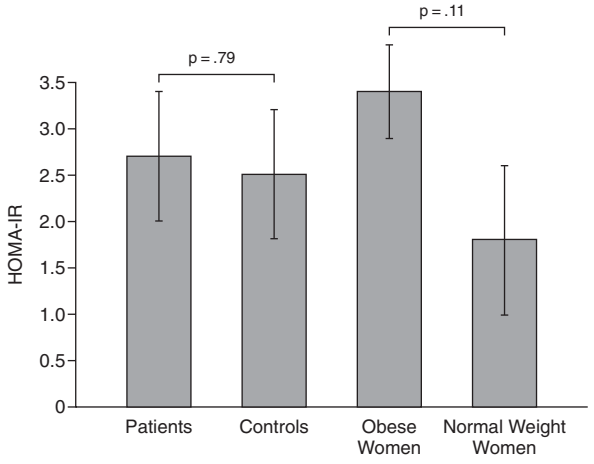
Of the 18 bipolar patients, 12 were considered obese (11 white and 1 African American; mean ± SEM duration of illness = 21.8 ± 2.6 years) by BMI criteria (mean ± SEM BMI = 35.2 ± 1.1 kg/m^2) and were well matched to obese controls (BMI = 34.0 ± 1.4 kg/m^2). Six bipolar patients (5 white and 1 African American; mean ± SEM duration of illness = 19.2 ± 5.0 years) and 5 controls were normal weight (BMI = 22.8 ± 0.7 vs. 23.2 ± 0.9 kg/m^2, respectively). Four obese bipolar patients and 6 obese controls were classified as postmenopausal, whereas 1 normal weight patient and 3 normal weight controls were postmenopausal. By design, all subjects were women. Of the bipolar patients, 12 subjects were treated with antipsychotic medications (aripriprazole, ziprasidone, haloperidol, quetiapine, or perphenazine), 17 with lithium and anticonvulsant medications (valproate, carbamazepine, lamotrigine, gabapentin, or topiramate), 5 with selective serotonin reuptake inhibitors (SSRIs: escitalopram, fluoxetine, or sertraline), 2 with a serotonin-norepinephrine reuptake inhibitor (venlafaxine), and 3 with benzodiazepines (lorazepam or clonazepam). Matched controls could never have been treated with any psychotropic medication, nor had they any previous history of mental illness. Two control subjects (1 obese and 1 normal weight) were treated with antihypertensive agents. By design, age, weight, and BMI were not different between groups (Table 1).

Table 1. Demographic Characteristics of 18 Women With DSM-IV Bipolar Disorder and 17 Matched Controls[a]

Characteristic	Patients, N = 18	Controls, N = 17	Obese Total, N = 24	Normal Weight Total, N = 11
Age, y	41.4 ± 2.1	40.9 ± 2.3	42.8 ± 1.7	39.5 ± 2.6
Weight, kg	82.1 ± 3.4	76.2 ± 3.7	94.0 ± 2.8	64.3 ± 4.2
BMI, kg/m^2	29.0 ± 0.9	28.6 ± 1.0	34.6 ± 0.8	23.0 ± 1.1
Race/ethnicity, N (%)				
White	16 (89)	16 (94)	22 (92)	10 (91)
African American	2 (11)	1 (6)	2 (8)	1 (9)

[a]Values represent mean ± SEM except where noted.
Abbreviation: BMI = body mass index.

Figure 1. Results of the Homeostatic Model Assessment of Insulin Resistance in 18 Women With DSM-IV Bipolar I Disorder and 17 Matched Controls[a]



[a]Error bars represent the SEM.
Abbreviation: HOMA-IR = Homeostatic Model Assessment of Insulin Resistance.

Insulin Resistance

Mean ± SEM insulin resistance was not different between patients (2.7 ± 0.7) and controls (2.5 ± 0.7, F = .07, df = 1, p = .79; Figure 1). No differences (interactions) were observed between obese patients and obese controls or normal weight patients and normal weight controls. Moreover, fasting glucose, HbA1c, and insulin levels were not different between patients and controls (Table 2). There was no significant difference observed in fasting glucose, HbA1c, or HOMA-IR between obese women and normal weight women, although a trend (p = .08) was observed in fasting insulin levels.

Blood Lipids and Blood Pressure

No differences were observed between patients and controls in respect to total cholesterol, LDL, VLDL or triglycerides, although a trend (p = .06) was observed for patients having lower HDL cholesterol than controls (Table 2). No significant differences were observed between patients and controls in respect to systolic and diastolic blood pressure. However, obese patients had significantly higher mean ± SEM systolic (142.2 ± 3.3 vs. 126.2 ± 3.3 mm Hg, F = 7.7, df = 1, p = .009) and diastolic (72.4 ± 1.5 vs. 65.1 ± 2.3 mm Hg, F = 14.0, df = 1, p = .001) blood pressure compared to obese controls. Normal weight patients were not more hypertensive than normal weight controls.

There were no significant differences in total or LDL cholesterol between obese and normal weight women, although obese women had significantly higher VLDL and triglyceride levels and lower HDL cholesterol than normal weight women. Additionally, systolic and diastolic blood pressure was significantly higher in obese women compared to normal weight women.

Whole Body Fat and Lean Mass

Patients were not different from controls in respect to mean ± SEM total body fat (40.3% ± 1.2% vs. 40.2% ± 1.2%, F = 0.004, df = 1, p = .95), and FM (34.8 ± 2.3 vs. 31.3 ± 2.4 kg, F = 1.1, df = 1, p = 0.31), although patients revealed a trend in higher FFM (44.8 ± 1.4 kg) compared to controls (41.1 ± 1.5 kg, F = 3.2, df = 1, p = .08). As expected, obese women had higher percentage body fat (47.8% ± 1.2% vs. 32.6% ± 1.4%, F = 79.0, df = 1, p = .001), FM (45.3 ± 1.9 vs. 20.9 ± 2.8 kg, F = 54.1, df = 1, p = .001), and FFM (45.9 ± 1.1 vs. 40.1 ± 1.7 kg, F = 8.0, df = 1, p = .008) compared to normal weight women.

Regional Fat Distribution Determined by Computed Tomography

Patients did not differ in total abdominal fat or SUB or VISC adiposity compared to matched controls. However, obese patients had more total mean ± SEM abdominal fat compared to obese controls (718.1 ± 35.1 cm^2 vs. 607.4 ± 33.6 cm^2, F = 4.5, df = 1, p = .04) (Figure 2A). Additionally, a trend was observed for obese patients to have more mean ± SEM VISC adiposity compared to matched controls (179.9 ± 13.0 cm^2 vs. 143.6 ± 12.5 cm^2, F = 3.8, df = 1, p = .06) (Figure 2B). There was no difference in total (261.3 ± 35.1 cm^2 and 332.7 ± 52.1 cm^2) or VISC (53.3 ± 17.6 cm^2 and 78.5 ± 19.3 cm^2) abdominal fat between normal weight bipolar patients or controls, respectively (Figures 2A and 2B). No differences were observed in SUB adiposity or IMAT in the thigh between patients and controls. Interactions between obese patients and obese controls or normal weight patients and normal weight controls were not observed.

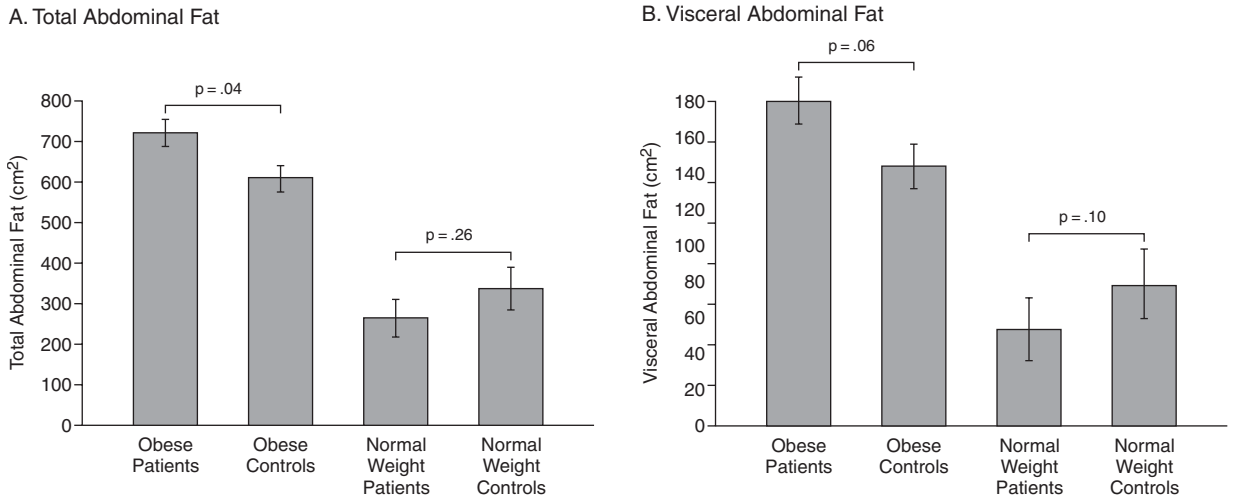
Obese women had more mean ± SEM total abdominal fat (662.7 ± 24.3 vs. 297.0 ± 35.3 cm^2, F = 73.0, df = 1, p = .001), SUB (245.0 ± 15.3 vs. 120.1 ± 22 cm^2,

Table 2. Metabolic Characteristics of 18 Women With DSM-IV Bipolar Disorder and 17 Matched Controls[a]

Characteristic	Patients	Controls	Obese Total	Normal Weight Total
Glucose, mmol/L	5.4 ± 0.2	5.4 ± 0.2	5.5 ± 0.1	5.3 ± 0.2
HbA1c	5.4 ± 0.4	6.4 ± 0.4	5.5 ± 0.3	6.3 ± 0.5
Insulin, μU/mL	10.7 ± 2.1	9.8 ± 2.3	13.0 ± 1.8	7.4 ± 2.6
Cholesterol, mg/dL	184.1 ± 10.8	203.1 ± 11.5	197.6 ± 8.8	189.6 ± 13.1
Low-density lipoprotein, mg/dL	105.5 ± 7.8	116.4 ± 8.2	117.9 ± 6.4	103.9 ± 9.3
Very low-density lipoprotein, mg/dL	16.3 ± 1.9	16.9 ± 2.0	20.6 ± 2.2*	12.6 ± 3.2
High-density lipoprotein, mg/dL	57.6 ± 3.8	68.6 ± 4.0	53.4 ± 3.1*	72.9 ± 4.6
Triglycerides, mg/dL	118.5 ± 19.5	100.7 ± 20.8	139.9 ± 15.9*	79.3 ± 23.6

[a]Values represent mean ± SEM.
*Significant difference between obese and normal weight women.
Abbreviation: HbA1c = glycosylated hemoglobin.

Figure 2. Abdominal Adiposity in 18 Women With DSM-IV Bipolar I Disorder and 17 Matched Controls[a]



[a]Error bars represent the SEM.

F = 21.6, df = 1, p = .001) and VISC abdominal fat (161.8 ± 9.0 vs. 65.9 ± 13.1 cm^2, F = 36.5, df = 1, p = .001), total thigh fat (197.1 ± 13.0 vs. 115.9 ± 19.0 cm^2, F = 12.5, df = 1, p = .001), SUB thigh fat (178.2 ± 12.8 vs. 103.1 ± 18.6 cm^2, F = 11.0, df = 1, p = .002) and IMAT fat (6.7 ± 05 vs. 1.5 ± 0.7 cm^2, F = 39.8, df = 1, p = .001) compared to normal weight women. When all subjects were combined, insulin resistance, defined by HOMA-IR, was associated with VISC fat (r^2 = 0.13, p = .04) and total abdominal SUB fat (r^2 = 0.12, p = .04). Total body fat was not associated with insulin resistance.

Energy Metabolism

No significant differences were observed in resting metabolic rate after accounting for the amount of fat free mass. Rates of fat oxidation, however, were lower in patients compared to controls (Table 3). Obese women did not differ from normal weight women in resting relative energy expenditure or relative and absolute rates of fat oxidation.

The fat oxidation during postabsorptive conditions was not related to insulin resistance. The activity monitors revealed that neither mean ± SEM total daily energy expenditure (2318.5 ± 68.8 vs. 2230.8 ± 74.6 kcal/24 hours; F = 0.74; df = 1, p = .40) nor energy expenditure during physical activity (418.0 ± 66.0 vs. 343.8 ± 71.5 kcal/24 hours; F = 0.58, df = 1, p = .45) was different between patients and controls, respectively. There were also no differences in mean ± SEM time spent in sedentary (21.4 ± 0.4 vs. 21.9 ± 0.5 hours; F = 0.50, df = 1, p = .49), moderate (1.0 ± 0.2 vs. 1.3 ± 0.2 hours; F = 0.94, df = 1, p = .34), or vigorous (0.18 ± 0.009 vs. 0.10 ± 0.010 minutes; F = 0.36, df = 1, p = .55) activity. No interactions were observed between obese patients and obese controls or normal weight patients and normal weight controls. Obese women expended slightly more mean ± SEM energy in the 24-hour period (2381.2 ± 57.5 vs. 2167.0 ± 83.6 kcal/24 hours, F = 4.4, df = 1, p = .05) compared to normal weight women. However, neither their total physical activity nor time

Table 3. Resting Energy Expenditure of 18 Women With DSM-IV Bipolar Disorder and 17 Matched Controls[a]

Value	Patients	Controls	Obese Total	Normal Weight Total
Energy expenditure, kcal/24 hr	1533.9 ± 51.4	1459.1 ± 54.7	1628.7 ± 42.0**	1364.4 ± 62.3
Energy expenditure, kg $FFM^{-1} \times min^{-1}$	34.4 ± 1.0	35.6 ± 1.1	35.7 ± 0.8	34.3 ± 1.2
Respiratory quotient	0.84 ± 0.01	0.82 ± 0.01	0.83 ± 0.009	0.84 ± 0.01
Fat oxidation, mg $FFM^{-1} \times min^{-1}$	1.3 ± 0.1*	1.7 ± 0.1	1.5 ± 0.1	1.5 ± 0.1
Fat oxidation, %	48.6 ± 3.8	56.9 ± 4.0	55.2 ± 3.1	50.3 ± 4.6
Carbohydrate oxidation, mg $FFM^{-1} \times min^{-1}$	3.2 ± 0.3	2.9 ± 0.3	2.8 ± 0.3	3.3 ± 0.2
Carbohydrate oxidation, %	51.4 ± 4.0	43.1 ± 4.0	44.8 ± 3.1	50.0 ± 4.6

[a]Values represent mean ± SEM.
*p < .05 between patients and controls.
**p < .05 between obese and normal weight women.
Abbreviation: FFM = fat-free mass.

Table 4. Energy Intake of 18 Women With DSM-IV Bipolar Disorder and 17 Matched Controls[a]

Value	Patients	Controls	Obese Total	Normal Weight Total
Total intake, kcal/24 hrs	2162.8 ± 252.3	1540.5 ± 268	1836.0 ± 206.0	1867.4 ± 305.5
Carbohydrate, g	260.2 ± 29.4.5	181.0 ± 31.3	206.7 ± 24.0	234.4 ± 35.6
Fat, g	95.2 ± 13.0	66.9 ± 13.8	84.8 ± 10.6	77.4 ± 15.7
Protein, g	76.5 ± 8.5	52.3 ± 9.1	63.9 ± 7.0	64.9 ± 10.3
Saturated fat, g	30.3 ± 4.0	21.0 ± 4.3	26.1 ± 3.3	25.3 ± 4.9
Carbohydrate, %	48.1 ± 2.1	47.3 ± 2.3	45.1 ± 1.8	50.4 ± 2.6
Fat, %	39.3 ± 1.9	38.0 ± 2.0	40.8 ± 1.6	36.5 ± 2.3
Protein, %	14.5 ± 0.6	13.9 ± 0.7	14.4 ± 0.5	14.0 ± 0.8
Sweets, %	16.2 ± 2.6	18.8 ± 2.8	16.6 ± 2.1	18.5 ± 3.1

[a]Values represent mean ± SEM.

spent in sedentary, moderate, or vigorous activities was higher.

Energy Intake and Macronutrient Composition

Total energy intake, fat intake and the percentage of fat, protein, carbohydrate, or sweets intake was similar in patients and controls (Table 4). Surprisingly, patients consumed more mean ± SEM servings of dairy (2.3 ± 0.3 vs. 1.1 ± 0.3, F = 9.7, df = 1, p = .004), grains (5.8 ± 0.8 vs. 3.1 ± 0.9, F = 4.5, df = 1, p = .043) and a trend for more vegetable servings (3.0 ± 0.4 vs. 2.1 ± 0.4, F = 3.1, df = 1, p = .087) in addition to significantly more calcium (1013.0 ± 87.8 vs. 539.0 ± 90.3 mg; F = 14.2, df = 1, p = .001) and fiber (17.5 ± 1.7 vs. 10.6 ± 1.8 g; F = 7.7, df = 1, p = .009) which have been associated with lower body weight.[37] Additionally, patients consumed less alcohol than controls (0.2% ± 0.7% vs. 3.2% ± 0.7% F = 12.8, df = 1, p = .001). Obese patients consumed a greater percentage of sweets (20.2% ± 3.0% vs. 13.0% ± 3.0%), although normal weight patients consumed less (12.3% ± 4.2% vs. 24.6% ± 4.6%, F = 6.6, df = 1, p = .02) compared to matched controls. There were no differences observed in total energy, carbohydrate, protein, fat, or fiber intake in obese or normal weight women when expressed as a percentage or in grams (Table 4). Obese women did not differ with respect to the percentage of fat, protein, carbohydrate, or sweets intake, although normal weight women consumed more mean ± SEM calcium (966.2 ± 108.3 vs. 687.7 ± 73.0 mg, F = 4.5, df = 1, p = .04) and servings of dairy (2.1 ± 0.3 vs. 1.3 ± 0.2 mg, F = 4.7, df = 1, p = .04) compared to obese women.

DISCUSSION

Individuals suffering from mental illness have a higher prevalence of obesity,[7,8,11,38] dyslipidemia,[17,18] hypertension,[7] cardiovascular disease,[7,19] and diabetes[13,15,16] than the general population. However, insulin resistance has not been fully characterized in these patients. It was reasonable, therefore, to examine whether patients with bipolar disorder were more insulin resistant than could be expected based on their level of obesity or adiposity.

One of the key findings of this study was that women with bipolar disorder were no more insulin resistant than race-, age-, and obesity-matched controls. One interpretation of this finding is that obesity may be the primary cause of insulin resistance and that bipolar disorder itself is not associated with insulin resistance independent of obesity. In other words, once these patients become

obese, they are no more insulin resistant than other obese women without bipolar disorder. Alternatively, there are several possibilities as to why differences in insulin resistance were not observed between patients and controls. Medications used by patients may have confounded the ability to detect differences in insulin sensitivity between patients and controls. Although we excluded patients with current or lifetime treatment with drugs that are known to alter insulin resistance, the effect on glucose metabolism is not clearly established for the majority of psychotropic medications. In addition, not all medications used to treat bipolar disorder exacerbate insulin resistance.[39–41] For instance, McIntyre et al.,[41] have suggested that some antidepressants may in fact improve insulin sensitivity. In their comprehensive review, these authors reported that some SSRIs reduced hyperglycemia and normalized glucose homeostasis, whereas nonselective monoamine oxidase inhibitors (MAOIs) were associated with hypoglycemia and an increased glucose disposal rate. Five bipolar patients in the current study were indeed treated with SSRIs, although no MAOIs were currently used in this population. It is therefore possible that these medications may have confounded our ability to detect small differences in insulin resistance between patients and controls, since these patients were treated with such medications prior to and during this study.

Another key finding in our study was that abdominal fat content, a strong correlate of insulin resistance,[42] was higher in obese patients compared to obese controls. This finding is in agreement with those of previous reports indicating that bipolar patients were more likely to have abdominal obesity than the general population.[7,8,11] For instance, Fagiolini et al.,[43] obtained waist circumference values of 171 patients with bipolar disorder. They reported that 49% of patients met criteria for abdominal obesity using waist circumference as the primary measure. Our data indicate that bipolar patients do indeed possess a key characteristic associated with insulin resistance. Although HOMA-IR, used in our study to quantify insulin resistance, is strongly correlated with direct measures of insulin resistance, this estimate of insulin resistance may not have been adequately sensitive to detect small differences in this relatively small number of bipolar patients. Future studies using more sophisticated techniques, such as hyperinsulinemic euglycemic clamps, to quantify insulin resistance in these patients are warranted. Another limitation was that only women were studied. It is possible that higher amounts of visceral abdominal fat in men with bipolar disorder would have allowed us to detect significant differences in insulin resistance in patients with bipolar disorder. Thus, similar studies should be conducted in men.

Large epidemiologic studies have revealed that the risk of insulin resistance rises in conjunction with the level of obesity (measured by BMI).[44] The obese women in our study tended ($p = .11$) to be more insulin resistant than normal weight women. Our study also revealed an association between insulin resistance and visceral adiposity but not with total body adiposity. It is possible that we were underpowered to detect significant associations between generalized adiposity and insulin resistance given the indirect assessment of insulin resistance. However, it has been well documented that abdominal adiposity is a much stronger predictor of insulin resistance than overall obesity.[45,46] Abdominal fat, therefore, very likely provides a better indicator of metabolic risk in this population than overall obesity. Indeed, future studies should be directed at examining the role of fat distribution in metabolic abnormalities in patients with bipolar disorder, not only generalized obesity.

Our data support the possibility that bipolar disorder itself or medications used to treat the disorder may indeed be eliciting increased weight gain through other physiologic mechanisms outside of energy balance. For instance, fat oxidation after an overnight fast, a correlate of insulin resistance in previous studies, was lower in patients compared to controls. This is the first study to show that bipolar patients utilize a lower proportion of fat during basal conditions compared to matched controls. A reduced capacity to utilize fat at rest has been linked to increased weight gain[26,47] and increased risk for insulin resistance.[27] This finding may provide important insight into factors that contribute to weight gain and obesity in patients with bipolar disorder. Additionally, we did not observe any differences in energy balance between patients and controls, supporting the possibility that a reduced-fat oxidation may be the primary culprit leading to excess weight in this population.

This is the first study that has examined energy expenditure in patients with bipolar disorder. Previous studies have examined physical activity levels in bipolar disorder using self-report measurements. For instance, Elmslie et al.[48] identified lifestyle-related factors through the Life in New Zealand activity questionnaire among patients with bipolar disorder and reference subjects matched for age and race for 4 weeks preceding study measurements. These authors reported that patients participated in fewer low-to-moderate intensity and high-intensity activities compared to reference subjects. In contrast, another study conducted by Davidson et al.[49] examined patients with mental illness defined as schizophrenia or schizoaffective or bipolar disorders. Authors examining participant self-reports from the Risk Factor Prevalence Survey[50] found that patients combined were more likely to walk for exercise compared to nonpatient participants. Although the participants in the previous 2 studies may have reported lower or higher exercise habits, neither study objectively measured 24-hour energy expenditure, which is an important factor to consider in respect to obesity. We did not observe any significant differences in total energy

expenditure or time spent in sedentary, moderate, or vigorous activities. On the other side of the spectrum, we did not observe any differences in energy intake or carbohydrate or fat consumption, although patients consumed over 600 more calories than controls. These results are in agreement with Elmslie et al.,[48] who used 24-hour diet recall and also a 4-day estimate of nutrient intake to report that women with bipolar disorder had higher energy intake, though not significantly, compared to reference subjects.

In conclusion, women with bipolar I disorder may not be more insulin resistant than age-, race- and BMI-matched controls. However, these patients had an overall worse cardiometabolic risk profile, including significantly more abdominal fat and higher blood pressure than controls. However, the lack of a direct measure of insulin resistance in this study, together with the likely confounding effects of medication use, does not completely rule out a more insulin-resistant phenotype in this population. Moreover, a reduced capacity to utilize fat as an energy substrate may predispose bipolar I patients to exacerbated weight gain with a concomitant increased risk for type 2 diabetes and cardiovascular disease.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), norepinephrine (Levophed and others), olanzapine (Zyprexa), quetiapine (Seroquel), sertraline (Zoloft and others), topiramate (Topamax), valproic acid (Depakene and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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