Low 24-Hour Adiponectin and High Nocturnal Leptin Concentrations in a Case-Control Study of Community-Dwelling Premenopausal Women With Major Depressive Disorder: The Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression (POWER) Study

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Objective: Major depressive disorder (MDD) is associated with immune system dysfunction and disruption of multiple circadian systems. Adiponectin is an adipocytokine with anti-inflammatory and antiatherogenic effects. Circulating concentrations are inversely related to adiposity and risks of metabolic syndrome and diabetes mellitus. Our goals were (1) to establish whether premenopausal women with MDD exhibit decreased plasma adiponectin concentrations and/or disruption of circadian adiponectin rhythmicity; (2) to assess whether there is a relationship between adiponectin and MDD; and (3) to explore the temporal relationships among adiponectin, leptin, corticotropin, and cortisol secretion.

Method: We conducted a case-control study of community-dwelling premenopausal women with *DSM-IV* MDD (n = 23) and age- and body mass index (BMI)–matched control subjects (n = 23). Main outcome measures were circulating concentrations of adiponectin, leptin, corticotropin, and cortisol measured hourly for 24 hours. Subjects were recruited from July 1, 2001, to February 28, 2003.

Results: Women with MDD had approximately 30% lower mean 24-hour concentration of adiponectin than did control subjects. Adiponectin concentration was inversely related to depression severity and total duration of disease, suggesting a causal link. In contrast, mean nocturnal leptin concentration was higher in the MDD versus control groups. Mean leptin concentration was inversely related to cortisol and adiponectin concentrations, both in subjects with depression and in control subjects. In cross-correlation analyses, the relationship between corticotropin and cortisol concentrations was stronger in women with MDD than in control subjects, a finding consistent with hypothalamic-pituitary-adrenal (HPA) axis activation in MDD.

Conclusions: In premenopausal women with MDD, reduced daily adiponectin production may increase the risk of diabetes mellitus, and elevated leptin may contribute to osteoporosis.

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Major depressive disorder (MDD) is a mood disorder with important consequences for the endocrine and immune systems. It affects approximately 17% of the general population, with increased morbidity due to central obesity, type-2 diabetes mellitus (T2DM), and cardiovascular disease (CVD).[1–4] Major depressive disorder is accompanied by disruption of the hypothalamic-pituitary-adrenal (HPA) axis[5] and disordered corticotropin secretion.[6] A disruption of circadian rhythms in MDD suggests that other endocrine systems are affected. The prevalences of T2DM and CVD are higher in subjects with MDD.[7] White adipose tissue, an organ with endocrine functions, secretes the adipocytokines, leptin, and adiponectin. Leptin was described in 1994 by positional cloning of the *ob* gene.[8] Leptin is produced in proportion to total body fat, and it signals to the central nervous system (CNS) the amount of energy stores to regulate food intake and energy expenditure.[9] If adequate body fat is present, energy can be expended for costly processes like reproduction and growth.[10] Leptin modulates several endocrine axes, including the HPA axis by negative feedback at the hypothalamus,[11] and elevated leptin has been associated with osteopenia.[12]

Adiponectin was first reported as an adipocyte secretory protein in 1995,[13] but only recently has its physiology been investigated. Plasma adiponectin concentrations are about 2 to 3 times greater than those of most other hormones, and its concentrations, unlike those of other adipocytokines, are inversely related to adiposity. Adiponectin receptors R1 (AdipoR1) and R2 (AdipoR2) have been identified in the periphery and CNS. Adiponectin receptor R1 is abundant in skeletal muscle, and AdipoR2 exists primarily in the liver. Adiponectin receptor R1 and AdipoR2 are also present in the paraventricular nucleus of the hypothalamus, amygdala, area postrema and, diffusely, in the periventricular areas and cortex.[2] AdipoR1, and AdipoR2 have been observed in the human pituitary as well.[14] Adiponectin inhibits gene expression and secretion of growth hormone (GH) and lutenizing hormone (LH) release in rat pituitary somatotropes and gonadotropes.[15] In human anterior pituitary cells, adiponectin expression has been observed in cells that produce GH, follicle-stimulating hormone (FSH), LH, and thyrotropin but not in corticotropin-producing cells.[14] Adiponectin has

generated interest in relation to obesity-related diseases. Pima Indians and Asian Indians with higher adiponectin are less likely to develop T2DM[16,17] because of enhanced glucose and fatty acid disposal by skeletal muscle.[18] Adiponectin is lower in patients with CVD,[19] and it prevents atherosclerotic progression by reducing smooth cell proliferation and improving angiogenesis and endothelial function.[20]

Leptin is a hormone produced by the white adipose tissue. Originally isolated by positional cloning, its discovery has prompted a new impetus in the field of the endocrinology of energy metabolism, and it has redefined the physiology of the adipose organ.[21] Leptin modulates appetite, food intake, sexual maturation and reproductive functions, and immune functions, all of which are disrupted in depression. We originally studied the rhythmicity of leptin and discovered that this adipocytokine is secreted in an exquisitely pulsatile fashion and that its secretion is inversely related to the secretion of corticotropin and cortisol.[23] Reports of serum leptin levels in depressed subjects are conflicting, with studies finding no differences, lower levels in depressed men, elevated levels in depressed men and women, or elevated levels only in depressed women.[22]

While leptin's rhythmicity is well described,[23] the 24-hour secretory profile of adiponectin is not well known. Adiponectin exhibits diurnal and ultradian rhythms in normal weight men.[24] Circulating concentrations of adiponectin have been reported in depressed patients, but only at single time points. In some studies, adiponectin was lower in newly diagnosed and drug-naive MDD subjects and was inversely related to depression severity.[25] However, in others, there was no significant relationship between single adiponectin measurements and depressive symptoms.[26] To date, 24-hour secretory profiles of adiponectin have not been described in MDD patients. Because MDD subjects have a higher CVD prevalence, and reduced adiponectin is associated with negative health consequences, adiponectin rhythmicity in patients with depression is of interest. The relationship of adiponectin to the HPA-axis and leptin also remains unknown in MDD subjects. Accordingly, the main goals of the current study were (1) to establish whether women with MDD have decreased circulating concentrations of adiponectin and/or disruption of adiponectin secretory rhythmicity; (2) to study the relationship of adiponectin and leptin secretion with depression; and (3) to explore the temporal correlations among circadian concentrations of adiponectin, leptin, corticotropin, and cortisol.

METHOD

Study Design

This ancillary study was performed as part of the Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression (POWER) study, a 36-month prospective study of bone turnover in 21- to 45-year-old premenopausal women with MDD conducted at the National Institutes of Health Clinical Center (NIH-CC).[4] Recruitment was conducted from July 1, 2001, to February 28, 2003, in Washington, DC, and the metropolitan area by newspaper, radio, Internet, and flyer advertisements among community-dwelling women. We enrolled 89 women with MDD and 44 healthy control subjects. Controls were matched to subjects with MDD based on a standard deviation from the mean of ± 3.0 years for age and of ± 2.0 kg/m^2 for body mass index (BMI). Subjects were seen at 0, 6, 12, 24, and 36 months.

Subjects

Major depressive disorder was diagnosed by 2 psychiatric clinicians using the Structured Clinical Interview (SCID) for *DSM-IV*[27] criteria. Women were enrolled if they met *DSM-IV* criteria for MDD and had experienced a depressive episode in the preceding 3 years, a limit chosen to minimize recall problems associated with remote depressive episodes. Exclusion criteria for women with MDD were suicidal risk, eating disorders, bipolar disorders, schizophrenia, and schizoaffective disorder. Patients with anxiety disorder or a history of alcohol or drug dependence in remission for 5 years were eligible. For controls, exclusion criteria were a history of any *DSM-IV* diagnosis other than past alcohol abuse.

From the whole POWER sample, we then individually matched 23 consecutively studied women with MDD with 23 control subjects, based on sample size analysis (see below). All participants were in good health, as assessed by medical history, physical examination, and screening evaluation (electrocardiogram, negative serum pregnancy test; tests of hematologic, thyroid, liver, and renal function). This study was approved by the Scientific Review Board and the Institutional Review Board of the NIMH. All participants provided written informed consent.

Psychiatric Assessment

Current severity of anxiety and depression was assessed using the Hamilton Anxiety Rating Scale (HARS, 14 questions) and the Hamilton Depression Rating Scale (HDRS, 24 questions). These 2 scales inquire about symptom severity over the past 2 weeks. As part of the SCID interview, we also inquired about age at onset, number and duration of the depressive episodes, current depressive state that met *DSM-IV* criteria, and antidepressant use.

Anthropometric Measurements

Weight was measured to the nearest 0.1 kg using a digital scale. Height was measured 3 times to the nearest 0.1 cm using a stadiometer. Waist circumference was measured at the level of the natural waist. Hip circumference was measured at the level of maximum extension of the buttocks. The mean of 3 measurements at each site was used in all analyses.

Cooper Test (12-Minute Walk/Run Test)

The Cooper test, an indirect index of physical fitness, was performed on the morning of the third admission day after completion of the blood collection. Performance was measured in total meters traversed within 12 minutes on a standardized treadmill.

Table 1. Demographic Characteristics of Women With MDD (n = 23) and Controls (n = 23)[a]

Characteristic	MDD Women (n = 23)	Control Women (n = 23)	*P* Value
Age, y	35 ± 6.0	35 ± 6.1	.76
Body mass index, kg/m^2	23.9 ± 3.9	24.5 ± 4.4	.68
Weight, kg	65.7 ± 11.2	69.2 ± 11.2	.37
Smoking, pack years	2.24 ± 3.8	2.56 ± 5.8	.84
Use of oral contraceptive, n/n	6/23	6/23	NA
Alcohol intake, g/d	5.7 ± 6.1	5.1 ± 3.4	.71
Caffeine intake, mg/d	240.5 ± 336.7	194.3 ± 170.4	.66
Cooper test (meters covered in 12 min)	1401 ± 426.0	1389 ± 278.4	.72

[a]Data are expressed as mean ± SD unless otherwise noted.
Abbreviations: MDD = major depressive disorder, NA = not applicable.

Table 2. Clinical Characteristics of Women With MDD (n = 23) and Controls (n = 23)[a]

Characteristic	MDD Women (n = 23)	Control Women (n = 23)
Current depression (within the last mo), n/n (%)	6/23 (26)	0
Lifetime history of depression, cumulative duration, mo	78 ± 84	NA
Hamilton Depression Rating Scale score	10 ± 7.3	2 ± 2.2
Hamilton Anxiety Rating Scale score	8 ± 5.9	1 ± 1.7
Age at onset, y	16 ± 8.4	NA
Use of psychiatric medications, n/n (%)	20/23 (87)	0
SSRI/SSNRI, n	17	0
Bupropion, n	2	0
Tetracyclic, n	1	0
Other Axis-I diagnoses, n/n (%)	16/23 (70)	2/23 (9)

[a]Data are expressed as mean ± SD unless otherwise noted.
Abbreviations: MDD = major depressive disorder, NA = not applicable, SSNRI = selective serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Dual Energy X-Ray Absorptiometry Dual energy x-ray absorptiometry (DXA) measurements for bone mineral density and body composition were performed by the Hologic DXA QDR 4500 (Hologic, Inc, Bedford, Massachusetts). Total body fat percent and abdominal area were reported from the T12/L1 interface to the L4/L5 interface, which includes visceral and subcutaneous fat.

Twenty-Four Hour Blood Sampling Protocol

Study participants were admitted to the NIH-CC in the late afternoon of the day before testing. All studies were performed after an overnight fast. Blood was collected via an intravenous catheter hourly from 0800 hours until 0800 hours the following morning, for a total of 25 samples. Plasma samples were saved at −80°C for subsequent measurements of adiponectin, leptin, corticotropin, and cortisol. The total amount of blood drawn from each subject was approximately 200 mL.

Hormone and Other Blood Measurements

Assays were performed blinded to group allocation. Intra-assay coefficients of variation (CVs) were < 15%. Hormones were measured as follows: plasma total adiponectin (Linco Research, St Charles, Missouri; radioimmunoassay [RIA]; sensitivity, 2 μg/mL; CV, 1.78%–6.21%); plasma leptin (Linco Research; RIA; sensitivity, 0.5 ng/mL; intra-assay CV, 8.3%). Plasma corticotropin was measured by chemiluminescent immunoassay using the Nichols Advantage apparatus (Nichols Institute Diagnostics, San Juan Capistrano, California). Serum insulin and cortisol were measured by chemiluminescent immunoassay using the DPC Immulite-2000 system (Diagnostics Product Corporation, Los Angeles, California). Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR).[28] Measurements of high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, total triglycerides, glucose, and insulin levels were performed on morning samples after an overnight fast.

Statistical Analyses

Circulating adiponectin concentrations that are reduced by 15%–33% are known to be predictive of later T2DM.[16,17] During the planning phase of this study, we conducted an analysis to determine the statistical power needed to detect a 15% difference in mean 24-hour adiponectin levels between groups and estimated that 23 subjects per group were needed ($P < .05$, 2-sided t test, power = 0.90; SD = 0.7).

Chronolab software (available from Universidade de Vigo, Vigo, Spain, Bioengineering & Chronobiology Laboratory, http://www.tsc.uvigo.es/BIO/) was used for cosinor analyses. By multiple regression analyses, we determined the relationship of adiponectin with measures of adiposity, clinical indices of depression, and with other hormones. Significance was accepted at a level of $P < .05$; all results are expressed as mean ± SD.

Cross-Correlation Analysis

To assess the temporal relationships of diurnal variations among hormones studied, we performed cross-correlation analyses on the following pairs of time series from each subject: corticotropin vs cortisol, leptin vs cortisol, and adiponectin vs leptin. The cross-correlation functions were then averaged for MDD subjects and controls, and the lag relationships of each pair were assessed. Mean correlation coefficients at any particular lag time were tested against the null hypothesis of no correlation by using Wilcoxon signed rank tests. The maximum correlation coefficients were compared between groups by using Wilcoxon 2-sample tests.

RESULTS

Demographic and Clinical Characteristics of Subjects

Demographic characteristics are reported in Table 1. The 2 groups did not differ in lifestyle characteristics examined. Table 2 illustrates the clinical characteristics of the MDD group. Women with MDD had a cumulative depression history of approximately 6 years. Mean age at onset was in the mid teens. Women with MDD on average exhibited mild symptoms of anxiety and depression, as indicated by HARS

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Table 3. Body Composition and Metabolic Characteristics of Women With MDD (n = 23) and Controls (n = 23)[a]

Characteristic	MDD Women (n = 23)	Control Women (n = 23)	*P* Value
Whole body lean mass, g	42,950 ± 4,850	45,260 ± 5,642	.1407
Whole body fat mass, g	19,640 ± 6,060	20,910 ± 4,613	.6565
Total mass, g	66,900 ± 11,050	70,450 ± 9,738	.4439
Total fat mass, %	28.8 ± 4.8	29.4 ± 3.6	.8210
Waist circumference, cm	77.5 ± 8.3	77.6 ± 8.2	.9697
Waist/hip ratio	0.76 ± 0.04	0.75 ± 0.05	.2861
HDL, mg/dL	57.0 ± 13.0	59.5 ± 12.8	.5715
LDL, mg/dL	107.4 ± 19.2	98.5 ± 19.5	.1537
Triglycerides, mg/dL	92.4 ± 45.5	75.8 ± 32.3	.1785
Total cholesterol, mg/dL	172.9 ± 23.3	165.9 ± 23.2	.3206
Fasting glucose, mg/dL	88.2 ± 7.7	86.6 ± 11.0	.494
Fasting insulin, μU/mL	6.4 ± 4.2	6.8 ± 5.2	.7427
HOMA-IR	1.4 ± 0.9	1.5 ± 1.4	.7034

[a]Data are expressed as mean ± SD unless otherwise noted.
Abbreviations: HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment for insulin resistance, LDL = low-density lipoprotein, MDD = major depressive disorder.

and HDRS scores. Six of 23 women with MDD were currently depressed, defined as an episode during the preceding 4 weeks. The majority of women with MDD were taking antidepressants. Two thirds had at least one other *DSM-IV* Axis I diagnosis.

Body Composition and Metabolic Features of Study Subjects

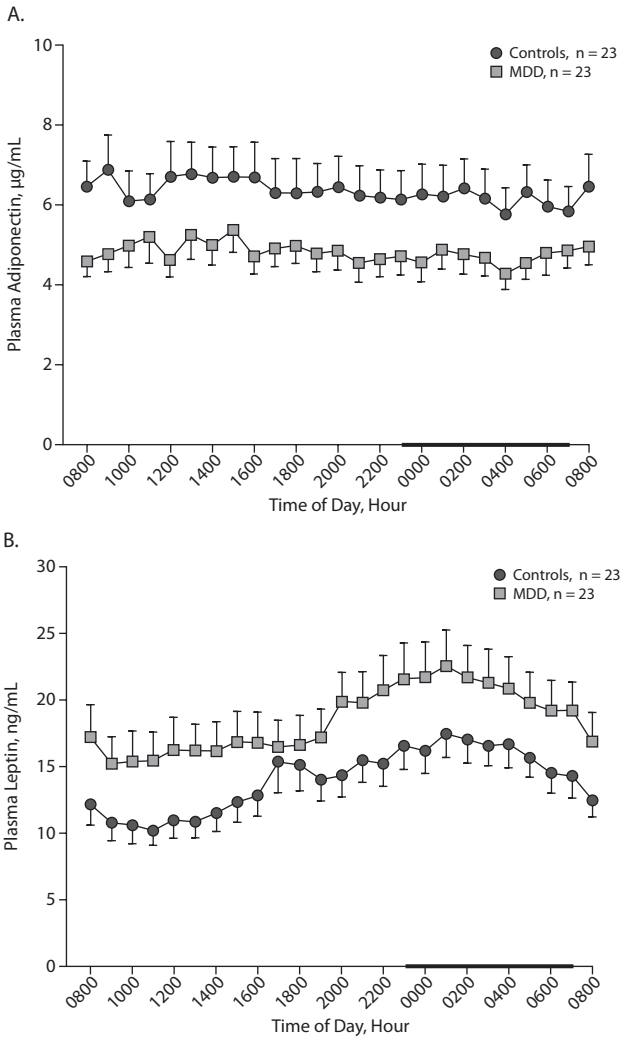
There were no significant differences in anthropometric measurements, body composition, lipid profiles, glucose, insulin, and insulin sensitivity (Table 3). However, women with MDD tended to have less lean mass than did controls. Total fat mass as measured by DXA, and waist-circumferences were similar. Women with MDD tended to have higher LDL, triglycerides, and total cholesterol levels. There were no differences in glucose or insulin levels or the HOMA-IR index between groups.

Twenty-Four Hour Hormonal Values

Figure 1, Table 4, and Table 5 illustrate mean adiponectin and leptin concentrations. In control subjects, diurnal fluctuation in adiponectin was about 30%. In both groups, mean adiponectin concentration was higher during the day, with a zenith occurring at approximately 1430 hours, an initial fall around 1600 hours, a further decline after 2300 hours, and then another increase at approximately 0300 hours. Women with MDD exhibited similar adiponectin rhythmicity. Mean adiponectin concentrations were about 25% lower at all 24-hour time points in women in the MDD versus control groups.

In both women with MDD and control subjects, leptin exhibited its typical diurnal variation, with higher concentrations during the night and a zenith at approximately 0200 hours. The lowest concentrations were observed during the day, with a nadir around 1100 hours. Mean leptin concentration was higher in women with MDD at all 24-hour time points. Leptin's rhythmicity was similar between groups.

Figure 1. Mean 24-Hour Plasma Adiponectin (A)[a] and Leptin (B)[b] Concentrations in Premenopausal Women With MDD (n = 23) and Controls (n = 23)[c]



[a]Adiponectin concentrations. In both groups, adiponectin exhibited a circadian variation characterized by slightly higher values during early afternoon with a peak around 1400h. Adiponectin remained lower in women with MDD over 24h. 0800h and 24h mean adiponectin was significantly lower in women with MDD compared to controls (0800h *P* adjusted for weight = .0053; mean 24h *P* adjusted for weight = .042; analysis of covariance).
[b]Leptin levels. In both groups, leptin exhibited a circadian variation characterized by a nocturnal zenith around 0200h and a nadir around 1000h. Leptin remained higher in women with MDD over 24h. 0800h and 24h mean leptin was significantly higher in women with MDD compared to controls (0800h *P* adjusted for weight = .010; mean 24h *P* adjusted for weight = .021; analysis of covariance). Mean nocturnal (2000h–0400h) leptin was greater in women with MDD than controls (21.05 ± 0.91 ng/mL vs 16.10 ± 0.98 ng/mL, respectively, *P* < .001).
[c]Error bars represent SEM.
Abbreviation: MDD = major depressive disorder.

Mean corticotropin and cortisol concentrations showed typical diurnal variations, with higher values in the morning (Figure 2A and 2B and Table 4). There were no differences in circadian corticotrophin secretion between groups; however, mean 0800-hour corticotropin concentration was somewhat higher in women with MDD than in control subjects (*P* = .0557).

Table 4. Circadian Characteristics of Adiponectin, Leptin, Corticotropin, and Cortisol Secretion in Women With MDD (n = 23) and Controls (n = 23)[a]

Characteristic	MDD Women (n = 23)	Control Women (n = 23)	*P* Value
Adiponectin, μg/mL			
Zenith (time of day)	1400 h	1430 h	NA
Nadir (time of day)	Not detected	Not detected	NA
Leptin, ng/mL			
Zenith (time of day)	1413 h	1343 h	NA
Nadir (time of day)	1048 h	1119 h	NA
Corticotropin, pg/mL			
0800 h	33.49 ± 19.1	24.73 ± 8.3	.0557
Zenith (time of day)	0700 h	0615 h	NA
Nadir (time of day)	1315 h	0000 h	NA
Cortisol, μg/mL			
0800 h	20.47 ± 7.7	20.74 ± 8.8	.8191
Zenith (time of day)	0800 h	0745 h	NA
Nadir (time of day)	1330 h	2430 h	NA

[a]Data are expressed as mean ± SD unless otherwise noted.
Abbreviations: MDD = major depressive disorder, NA = not applicable.

Table 5. Adiponectin and Leptin Concentrations in Women With MDD (n = 23) and Controls (n = 23)[a]

Concentration	MDD Women (n = 23)	Control Women (n = 23)	*P* Value	
			Unadjusted	Adjusted by Weight (kg)[b]
Adiponectin, μg/mL				
0800 hours	4.6 ± 1.9	6.5 ± 2.9	.013*	.0053*
24-hour	4.8 ± 2.34	6.3 ± 3.3	.080	.047*
1300–1600 hours	5.1 ± 2.5	6.7 ± 3.7	.089	.047*
2100–2400 hours	4.6 ± 2.4	6.2 ± 3.3	.075	.045*
Leptin, ng/mL				
0800 hours	17.1 ± 9.2	12.1 ± 6.5	.065	.010*
24-hour	18.3 ± 8.6	13.9 ± 6.3	.095	.021*
1300–1600 hours	21.5 ± 9.6	16.9 ± 7.4	.12	.026*
2100–2400 hours	15.5 ± 8.6	10.5 ± 5.5	.047*	.006*

[a]Data expressed as mean ± SD unless otherwise noted.
[b]Analysis of covariance.
*Statistically significant ($P < .05$).
Abbreviation: MDD = major depressive disorder.

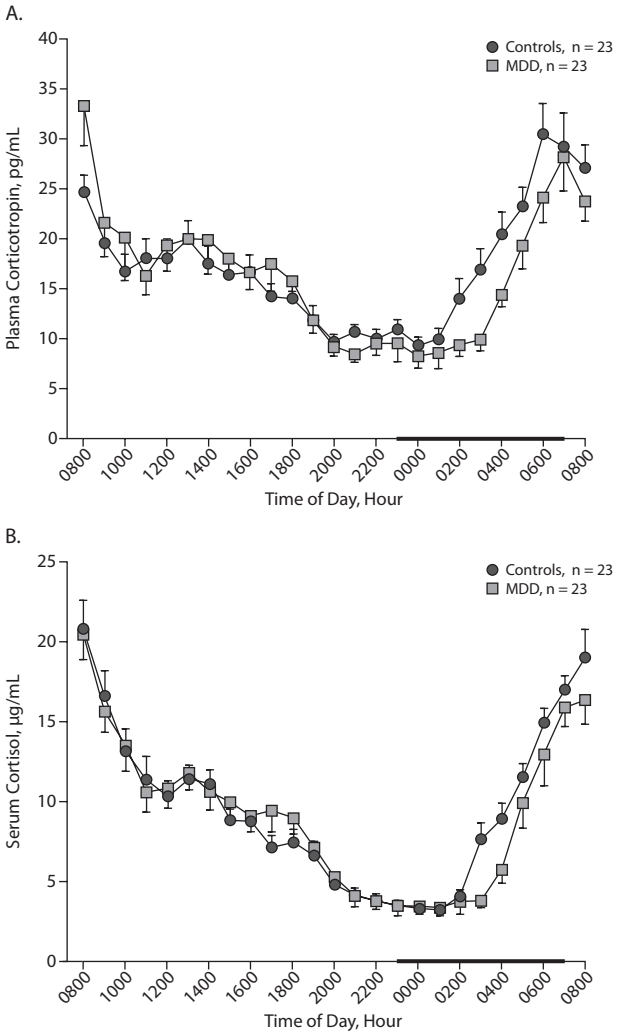
Relationships of Adiponectin With Adiposity and Clinical Indices of Depression

The diagnosis of MDD accounted for approximately 25%–30% of the variability in adiponectin concentrations (0800-hour adiponectin, R^2 0.285; $P = .004$; 24-hour mean adiponectin concentration, $R^2 = 0.267$; $P = .001$). Adiponectin concentration was inversely related to the cumulative duration of depression ($R = -0.51$; $P = .03$) and tended to be inversely related to the duration and severity of depression ($R = -0.41$; $P = .09$). Adiponectin concentration accounted for approximately 20% of the waist-hip ratio variability (0800-hour adiponectin, $R^2 = 0.194$; $P = .002$; 24-hour mean adiponectin concentration, $R^2 = 0.230$; $P = .007$). Adiponectin concentration and waist-hip ratio were inversely related ($R = -0.57$; $P = .04$). No colinearity was observed between MDD and waist-hip ratio.

Temporal Relationship of Adiponectin, Leptin, Corticotropin, and Cortisol

Corticotropin and cortisol exhibited similar secretion with a zenith in the early morning and nadir in the afternoon.

Figure 2. Mean 24-Hour Plasma Corticotropin (A)[a] and Serum Cortisol (B)[b] Concentrations in Premenopausal Women With MDD (n = 23) and Controls (n = 23)[c]



[a]Corticotropin concentrations collected hourly for 24h starting at 0800h in women with MDD and in controls individually age- and BMI-matched. Lights were off between 2300h–0700h, as indicated by the bold horizontal line on the x axis. In both groups, corticotropin exhibited similar circadian rhythm with similar time of peak and nadir. 0800h Corticotropin was higher in women with MDD than controls. Mean nocturnal (0100h–0500h) Corticotropin was lower in women with MDD than controls ($P = .023$).
[b]Cortisol concentrations. In both groups, cortisol exhibited similar circadian rhythm and no difference in peak values.
[c]Error bars represent SEM.
Abbreviations: BMI = body mass index, MDD = major depressive disorder.

As expected, the cortisol peak followed the corticotropin peak with a time lag of < 1 hour. Leptin secretion was almost directly inverse to those of corticotropin and cortisol. Overall, temporal relationships were not different between the MDD and control groups.

Cross-Correlation Analysis

Table 6 reports cross-correlations, including mean maximum coefficients of correlation, for various comparisons of 2 hormones as a paired time series. Corticotropin vs cortisol was related (mean maximum correlation: controls; $r = .739$,

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Table 6. Cross-Correlation Analysis for Various Comparisons of 2 Hormones as a Paired Time-Series in Women With MDD and Controls

		Women With Major Depressive Disorder				Control Women				
		Lag Time With Maximum Cross-Correlation	Maximum Correlation Coefficient			Lag Time With Maximum Cross-Correlation	Maximum Correlation Coefficient			
			Mean	SD	*P* Value*		Mean	SD	*P* Value*	*P* Value**
Corticotropin	Cortisol	0	0.819	0.092	< .001	0	0.739	0.128	< .001	.018
Leptin	Cortisol	−2	−0.531	0.210	< .001	−2	−0.509	0.194	< .001	.556
Leptin	Adiponectin	3	−0.273	0.188	< .001	0	−0.254	0.398	.008	1.000

*Wilcoxon signed rank test, H_0: $r = 0$.
**Wilcoxon 2-sample test, comparing control women and women with major depressive disorder.
Symbol: H_0 = the null hypothesis.

$P < .001$; MDD: $r = .819$, $P < .001$), and this relationship was stronger in women with MDD than in controls ($P = .018$).

Corticotropin versus cortisol secretion was synchronized with a lag of 0 hours (ie, an increase in corticotropin concentration was followed by an increase in cortisol concentration within 0 minutes to 1 hour). The maximum cross-correlation was observed at 0 minutes lag time in both groups.

Leptin versus cortisol concentration was inversely related in the MDD ($r = -0.519$, $P < .001$) and control groups ($r = -0.531$, $P < .001$). The maximum cross-correlation was observed at −2 hours' lag time. Leptin versus adiponectin concentration was weakly but significantly related (controls $r = -0.273$, $P < .001$; MDD: $r = -0.254$, $P < .008$). There were no significant differences in the leptin-cortisol, or leptin-adiponectin relationships between the MDD and control groups.

DISCUSSION

Premenopausal women with MDD exhibited lower circadian plasma adiponectin concentrations than did closely matched control subjects. As reduced adiponectin has been shown to predict T2DM and CVD, premenopausal women with MDD may be at increased risk for both conditions. Women with MDD also had increased nocturnal leptin, elevated morning corticotropin, and decreased nocturnal corticotropin and cortisol. Corticotropin *and* cortisol were more strongly related in women with MDD than in control subjects, suggesting HPA-axis activation in depression.

Adiponectin

In the current study, women with MDD exhibited adiponectin concentrations that were reduced by an average of 25%, a magnitude of decrease that has been reported in prospective studies to increase the risk of T2DM and CVD.[16,17,29] Our findings suggest that otherwise healthy premenopausal women with MDD may form a distinct subgroup at risk for these conditions. Lower adiponectin was related to increased severity of depression. Consistent with the current study, single adiponectin measurements were decreased in newly diagnosed MDD subjects and were inversely related to depression severity.[25] Men with MDD also tended to have lower adiponectin than did controls.[26] Our findings contrast, however, with data from 2 other reports.[30,31] Both evaluated older populations, and one utilized broad inclusion criteria for depression and did not exclude subjects with comorbid illnesses. Different ethnicity may also have played a role, as one study was conducted in a Chinese population.[30]

While lower circadian adiponectin concentration was not associated in this study with altered insulin sensitivity or metabolic alterations, there was a trend toward increased LDL and triglyceride levels in women with MDD. These findings might not have reached statistical significance because of the relatively small sample size or insufficient time to develop metabolic alterations. As previously reported, this same cohort of women exhibited increased evening levels of factor VIII and plasminogen activator inhibitor-1, 2 markers of enhanced cardiovascular risk[4]; increased levels of C-reactive protein, a marker of inflammation[32]; an increase in 24-hour circulating proinflammatory cytokines and a decrease in anti-inflammatory cytokines.[33] The POWER study and the current substudy, are notable in that several related variables were concurrently measured, adding validity to these results. However, given the cross-sectional nature of this report, we cannot establish whether decreased adiponectin concentrations were due to depression per se, to nonspecific lifestyle factors, or to antidepressant medications. Most of the women with MDD were taking selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-norepinephrine reuptake inhibitors (SSNRIs). Selective serotonin reuptake inhibitors and SSNRIs may act to increase adiponectin secretion from adipocytes. Patients with remitted depression who received 6 months of SSRI therapy have been reported to have higher adiponectin levels than those in healthy controls.[34] It is of note, therefore, that our sample of women with MDD had *lower* adiponectin concentrations than those in healthy controls, *in spite of* their being on SSRI therapy.

To our knowledge, this is the first report describing the circadian rhythm of adiponectin in women with MDD. Women with MDD had lower adiponectin around the clock, but no differences were observed between MDD and control groups in time of the peak or amplitude. More frequent sampling may have unraveled more subtle differences between the groups. A rhythm of adiponectin secretion characterized by higher values during the day with a peak in the late morning was originally reported in healthy men.[22] Adiponectin's rhythmicity has also been studied in obese patients, in whom rhythmicity was preserved but there were higher daytime levels.[35,36]

It is possible that, in women with MDD, short sleep and/or sleep disruption decreased adiponectin secretion. Sleep disturbances are one of the components of the depressive syndrome, according to *DSM-IV* criteria, and approximately 60% of depressed patients have insomnia.[37] In the Nurses Health Study Cohort,[38] women with more frequent snoring, a proxy for sleep disruption, had proportionally lower adiponectin levels. Sleep-deprived men lose the typical day/night variations in adiponectin.[39]

Leptin

Women with MDD had approximately 25% higher concentrations of leptin than those in healthy controls and exhibited the typical nocturnal rise in leptin concentrations.[23] Because MDD is a state of increased sympathetic tone,[40] higher leptin may have been secondary to activation of the sympathetic nervous system, which is known to stimulate leptin secretion. We have previously shown that this group of women with MDD has clinically relevant lower bone mass and that depression is a risk factor for osteoporosis comparable in magnitude to other well-established risk factors.[3] Leptin has been shown in a mouse model to centrally inhibit bone formation via the sympathetic system. Apposition of new bone takes place mostly at night, as indicated by circadian measurements of markers of bone turnover[41]; therefore, higher nocturnal leptin levels may contribute to the development of osteoporosis in women with MDD.

HPA Axis

As expected, corticotropin and cortisol concentrations were strongly related, and this correlation was more pronounced in MDD subjects. These findings support MDD as a state of HPA axis activation and validate the notion that subtle alterations in the HPA axis are present in mild depression. Women with MDD exhibit diminished negative feedback of cortisol on corticotropin.[42] The activation of the HPA axis in MDD subjects is caused in part by relative cortisol resistance at the glucocorticoid receptor.[43] We previously reported that women with MDD were more likely to be homozygous for a glucocorticoid receptor polymorphism, resulting in higher sensitivity to dexamethasone.[44]

In the current study, lower nocturnal corticotropin and cortisol concentrations were associated with increased nocturnal leptin concentrations. Leptin and cortisol were strongly and inversely correlated in both MDD and control groups. Elevated leptin may have decreased nocturnal corticotropin and cortisol levels via inhibition of the hypothalamic–corticotrophin-releasing hormone neuron.[23]

Overall Clinical Relevance

We propose that this sample of women with MDD is representative of a distinct clinical phenotype that is emerging, characterized by an increased risk for insulin resistance, cardiovascular disease, and osteopenia. By use of sensitive analytic techniques and around-the-clock measurements, we have described a novel hormonal and immune profile that may enhance our understanding of the neuroendocrinology of major depression. In this study of adipocytokines, we found that women with MDD had decreased diurnal adiponectin concentrations, of sufficient magnitude to put them at elevated risk for T2DM. We have previously shown that this same cohort exhibits elevated circulating concentrations of Factor VIII and plasminogen activator inhibitor-1, and it may be at increased risk for thromboembolic events.[4] Decreased adiponectin levels have also been implicated in CVD, and we have found changes in other markers related to CVD risk. Our study cohort also had alterations in the immune system, characterized by an increase in proinflammatory and a decrease in anti-inflammatory cytokines evident both in 24-hour plasma cytokines[3] and in cytokine secreted in sweat,[33] as well as increases in C-reactive protein, a well-accepted marker of inflammation.[32] Although our MDD patients were not overtly hypercortisolemic, we identified subtle alterations in their HPA-axis function that may be partly related to genetic polymorphisms of the glucocorticoid receptor that we previously reported.[44] Finally, this investigation on adipocytokines demonstrated that women with MDD exhibit elevated nocturnal leptin levels. Leptin has emerged as one regulator of bone formation through actions on osteoblasts, and it may account for bone deficits in women with MDD [3]. These alterations in endocrine and immune systems, taken together, provide possible mechanisms for several of the medical consequences of depression, including insulin resistance, CVD, and osteopenia.

Strengths and Limitations

The current study had several strengths. The sample was well characterized from a metabolic and hormonal perspective; measurements of multiple hormones and immune outcomes were performed hourly over 24 hours; and the sample size was adequately powered. According to one large, recent survey,[45] 50.5% of men and 65.5% of women with MDD are pharmacologically treated. The adjusted odds ratio for a subject with MDD to have had generalized anxiety disorder in the previous 12 months increased severalfold to 8.6.[45] Therefore, our sample may be representative of a large proportion of the general population. At the same time, because of these confounding factors we cannot absolutely attribute our findings to MDD per se versus concomitant medications and comorbidity.

Limitations included the cross-sectional nature of this analysis. The clinical sample was composed mainly of white women, and most subjects had mild depression. Hourly sampling did not allow for more detailed analysis of circadian secretion. Most of our subjects were pharmacologically treated and suffered from comorbid generalized anxiety disorder and other *DSM-IV* diagnoses.

Future Research Questions

Future studies appear warranted to establish whether a causal link exists between MDD and decreased daily production of adiponectin. These studies should be large enough

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and of sufficient duration to detect clinical events such as T2DM or CVD. The effects of antidepressants on adiponectin should be investigated, as should the mechanisms that lead to decreased adiponectin and increased leptin secretion, respectively.

CONCLUSIONS

We report herein decreased adiponectin and elevated leptin concentrations in premenopausal women with MDD. These changes in adipocytokines are of large magnitude, potentially clinically significant, and generalizable to the large population of young women who have mild depressive symptoms and who are on treatment. Given the high prevalence and chronic nature of depression, especially in women, and the increasing recognition of adiponectin as a risk factor for T2DM, these data are likely to have public health significance.

Drug name: bupropion (Aplenzin, Wellbutrin, and others).

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REFERENCES

1. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry*. 2005;58(3):175–189.
2. Ahima RS, Qi Y, Singhal NS, et al. Brain adipocytokine action and metabolic regulation. *Diabetes*. 2006;55(suppl 2):S145–S154.
3. Eskandari F, Martinez PE, Torvik S, et al. Premenopausal, Osteoporosis Women, Alendronate, Depression (POWER) Study Group. Low bone mass in premenopausal women with depression. *Arch Intern Med*. 2007;167(21):2329–2336.
4. Eskandari F, Mistry S, Martinez PE, et al. POWER (Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression) Study Group. Younger, premenopausal women with major depressive disorder have more abdominal fat and increased serum levels of prothrombotic factors: implications for greater cardiovascular risk. *Metabolism*. 2005;54(7):918–924.
5. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA*. 1992;267(9):1244–1252.
6. Young EA, Veldhuis JD. Disordered adrenocorticotropin secretion in women with major depression. *J Clin Endocrinol Metab*. 2006;91(5):1924–1928.
7. Kessler RC, McGonagle KA, Zhao SY, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8–19.
8. Zhang YY, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372(6505):425–432.
9. Robertson SA, Leinninger GM, Myers MG Jr. Molecular and neural mediators of leptin action. *Physiol Behav*. 2008;94(5):637–642.
10. Ahima RS, Prabakaran D, Mantzoros C, et al. Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996;382(6588):250–252.
11. Heiman ML, Ahima RS, Craft LS, et al. Leptin inhibition of the hypothalamic-pituitary-adrenal axis in response to stress. *Endocrinology*. 1997;138(9):3859–3863.
12. Iwamoto I, Douchi T, Kosha S, et al. Relationships between serum leptin level and regional bone mineral density, bone metabolic markers in healthy women. *Acta Obstet Gynecol Scand*. 2000;79(12):1060–1064.
13. Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem*. 1995;270(45):26746–26749.
14. Psilopanagioti A, Papadaki H, Kranioti EF, et al. Expression of adiponectin and adiponectin receptors in human pituitary gland and brain. *Neuroendocrinology*. 2009;89(1):38–47.
15. Rodriguez-Pacheco F, Martinez-Fuentes AJ, Tovar S, et al. Regulation of pituitary cell function by adiponectin. *Endocrinology*. 2007;148(1):401–410.
16. Lindsay RS, Funahashi T, Hanson RL, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet*. 2002;360(9326):57–58.
17. Snehalatha C, Mukesh B, Simon M, et al. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. *Diabetes Care*. 2003;26(12):3226–3229.
18. Fruebis J, Tsao TS, Javorschi S, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci U S A*. 2001;98(4):2005–2010.
19. Iwashima Y, Katsuya T, Ishikawa K, et al. Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension*. 2004;43(6):1318–1323.
20. Hopkins TA, Ouchi N, Shibata R, et al. Adiponectin actions in the cardiovascular system. *Cardiovasc Res*. 2007;74(1):11–18.
21. Friedman JM. Leptin at 14 y of age: an ongoing story. *Am J Clin Nutr*. 2009;89(3):973S–979S.
22. Cizza G, Primma S, Csako G. Depression as a risk factor for osteoporosis. *Trends Endocrinol Metab*. 2009;20(8):367–373.
23. Licinio J, Mantzoros C, Negrão AB, et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. *Nat Med*. 1997;3(5):575–579.
24. Gavrila A, Peng CK, Chan JL, et al. Diurnal and ultradian dynamics of serum adiponectin in healthy men: comparison with leptin, circulating soluble leptin receptor, and cortisol patterns. *J Clin Endocrinol Metab*. 2003;88(6):2838–2843.
25. Leo R, Di Lorenzo G, Tesauro M, et al. Decreased plasma adiponectin concentration in major depression. *Neurosci Lett*. 2006;407(3):211–213.
26. Hung YJ, Hsieh CH, Chen YJ, et al. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. *Clin Endocrinol (Oxf)*. 2007;67(5):784–789.
27. First MB, Spitzer RL, Gibbon M, et al: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P), Version 2.0. New York, NY: Biometrics Research, New York State Psychiatric Institute; August 1998.
28. Turner RC, Holman RR, Matthews D, et al. Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism*. 1979;28(11):1086–1096.
29. Lim S, Koo BK, Cho SW, et al. Association of adiponectin and resistin with cardiovascular events in Korean patients with type 2 diabetes: the Korean atherosclerosis study (KAS): a 42-month prospective study.

Atherosclerosis. 2008;196(1):398–404.
30. Pan A, Ye X, Franco OH, et al. The association of depressive symptoms with inflammatory factors and adipokines in middle-aged and older Chinese. *PLoS ONE*. 2008;3(1):e1392.
31. Narita K, Murata T, Hamada T, et al. Adiponectin multimer distribution, not absolute amount of plasma, correlates with depression severity in healthy elderly subjects. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(1):124–127.
32. Cizza G, Eskandari F, Coyle M, et al. Plasma CRP Levels in Premenopausal Women with Major Depression: a 12-Month Controlled Study. *Horm Metab Res*. 2009;41(8):641–648.
33. Cizza G, Marques AH, Eskandari F, et al. POWER Study Group. Elevated neuroimmune biomarkers in sweat patches and plasma of premenopausal women with major depressive disorder in remission: the POWER study. *Biol Psychiatry*. 2008;64(10):907–911.
34. Narita K, Murata T, Takahashi T, et al. Plasma levels of adiponectin and tumor necrosis factor-alpha in patients with remitted major depression receiving long-term maintenance antidepressant therapy. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(6):1159–1162.
35. Calvani M, Scarfone A, Granato L, et al. Restoration of adiponectin pulsatility in severely obese subjects after weight loss. *Diabetes*. 2004; 53(4):939–947.
36. Yildiz BO, Suchard MA, Wong ML, et al. Alterations in the dynamics of circulating ghrelin, adiponectin, and leptin in human obesity. *Proc Natl Acad Sci U S A*. 2004;101(28):10434–10439.
37. Ohayon MM. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *J Psychiatr Res*. 1997;31(3):333–346.
38. Williams CJ, Hu FB, Patel SR, et al. Sleep duration and snoring in relation to biomarkers of cardiovascular disease risk among women with type 2 diabetes. *Diabetes Care*. 2007;30(5):1233–1240.
39. Shea SA, Hilton MF, Orlova C, et al. Independent circadian and sleep/wake regulation of adipokines and glucose in humans. *J Clin Endocrinol Metab*. 2005;90(5):2537–2544.
40. Gold PW, Wong ML, Goldstein DS, et al. Cardiac implications of increased arterial entry and reversible 24-h central and peripheral norepinephrine levels in melancholia. *Proc Natl Acad Sci U S A*. 2005;102(23):8303–8308.
41. Hassager C, Risteli J, Risteli L, et al. Diurnal variation in serum markers of type I collagen synthesis and degradation in healthy premenopausal women. *J Bone Miner Res*. 1992;7(11):1307–1311.
42. Young EA, Carlson NE, Brown MB. Twenty-four-hour ACTH and cortisol pulsatility in depressed women. *Neuropsychopharmacology*. 2001;25(2):267–276.
43. Young EA, Haskett RF, Murphy-Weinberg V, et al. Loss of glucocorticoid fast feedback in depression. *Arch Gen Psychiatry*. 1991;48(8):693–699.
44. Krishnamurthy P, Romagni P, Torvik S, et al. P.O.W.E.R. (Premenopausal, Osteoporosis Women, Alendronate, Depression) Study Group. Glucocorticoid receptor gene polymorphisms in premenopausal women with major depression. *Horm Metab Res*. 2008;40(3):194–198.
45 . Hasin DS, Goodwin RD, Stinson FS, et al. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry*. 2005; 62(10):1097–1106.

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