Overweight and Obesity Affect Treatment Response in Major Depression

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Background: Epidemiologic and clinical studies suggest comorbidity between major depressive disorder (MDD) and obesity. To elucidate the impact of weight on the course of depression beyond comorbidity, we investigated psychopathology, attention, neuroendocrinology, weight change, and treatment response in MDD patients, depending on their weight.

Methods: Four hundred eight inpatients with MDD participated in the Munich Antidepressant Response Signature Study, designed to discover biomarkers and genotypes that are predictive for clinical outcome. Psychopathology and anthropometric parameters were monitored weekly in 230 patients. In subsamples, combined dexamethasone–corticotropin-releasing hormone and attention tests were conducted at admission and discharge. One thousand twenty-nine diagnosed matched controls served for morphometric comparisons.

Results: Patients with MDD had a significantly higher body mass index (BMI) compared with healthy controls. Patients with high BMI ($\geq$25) showed a significantly slower clinical response, less improvement in neuroendocrinology and attention, and less weight gain than did patients with normal BMI (18.5 $\leq$ BMI $<$ 25) during antidepressant treatment.

Conclusions: Our findings suggest that overweight and obesity characterize a subgroup of MDD patients with unfavorable treatment outcome.

Key Words: Antidepressant treatment, attention, depression, dex-CRH test, obesity, overweight, weight change

Major depressive disorder (MDD) and obesity are major public health problems that have had increasing prevalence during the last decades (Baskin *et al.* 2005; Stover *et al.* 2003). Epidemiologic and clinical studies suggest a comorbidity between depression and obesity (Faith *et al.* 2002; McElroy *et al.* 2004; Simon *et al.* 2006; Stunkard *et al.* 2003), although in some studies this association is restricted to the subtype of atypical depression (Hasler *et al.* 2004; Kendler *et al.* 1996). Dysregulation of the hypothalamus-pituitary-adrenocortical (HPA) axis, impaired function of glucocorticoid receptors (GRs; Holsboer 2000; Ljung *et al.* 2002; Salehi *et al.* 2005), and disturbances in central serotonin, norepinephrine, and dopamine neurotransmitter systems (Bjorntorp and Rosmond 2000) have been identified in both depression and obesity. Several factors have been discussed as potential contributors to a high interindividual difference in response to antidepressants, but efficient clinical predictors have not yet been identified. In this context, obesity was described as a risk factor for resistance to fluoxetine treatment in an outpatient study (Papakostas *et al.* 2005). Furthermore, many studies have analyzed weight changes during psychopharmacological therapy with a medication-based approach (Aronne and Segal 2003), though only a few focus on other mediating factors. Patients with MDD frequently show impairments in attention and executive functions (Cohen *et al.* 2001; Majer *et al.* 2004; Zihl *et al.* 1998), whereas there is only little evidence for impaired cognition in obese persons (Elias *et al.* 2003).

The aim of our study was to elucidate the effects of weight status in MDD patients on psychopathology, treatment response, neuroendocrinology, weight change, and cognitive function during antidepressant treatment.

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Methods and Materials

Subjects

Four hundred eight inpatients (female, n = 228; male, n = 180; mean age, 47.8 ± 14.3 y) participated in the Munich Antidepressant Response Signature project (Binder *et al.* 2004). Patients were diagnosed according to the DSM-IV (American Psychiatric Association 1994) criteria. Depressive disorders caused by a medical or neurologic condition and alcohol or substance dependence were exclusion criteria. One thousand twenty-nine controls were selected randomly from a Munich-based community sample and were screened for the absence of anxiety and affective disorders by using the screening version of the M-CIDI (Wittchen *et al.* 1999). Individuals were included after details of the study were explained and written informed consent was obtained. The local ethics committee of the Ludwig Maximilians University (Munich, Germany) approved the study. Psychopathology was assessed by trained raters by using the 21-item Hamilton Depression rating (HAM-D) scale within 5 days of admission and in weekly intervals. Patients were treated according to doctor's choice with different antidepressants. Dosages of antidepressants were aligned to therapeutic ranges via plasma concentrations of antidepressants that were monitored weekly. Patients were weighed at admission and in weekly intervals. Body mass index [BMI, in kg/m^2; weight/(height)^2] values in patients (n = 408) at admission ranged from 14.97 to 46.21. For analyses within the patient group, individuals who were underweight (BMI of $<$18.5; Centers for Disease Control and Prevention 2005) or had HAM-D score of lower than 18 at admission were excluded. We divided the remaining 320 patients into two groups: normal BMI (BMI $\leq$ 25; n = 173; mean ± SD, 22.10 ± 1.7) and high BMI (BMI $>$ 25; n = 147; mean ± SD, 28.50 ± 2.9). Patients' characteristics are shown in Table 1.

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Table 1. Patient Characteristics and Psychopathology

Patient Characteristics	BMI ≤ 25 (n = 173)	BMI > 25 (n = 147)	F	p Value
Percentage Data				
Gender (% male patients)	35.80	55.10	—	<.001[c]
Suicide Ideation (% of patients)	38.02	28.89	—	.18
Suicide Attempts	23.26	23.29	—	.99
Therapy Resistance	12.28	16.78	—	.26
Psychotic Symptoms	13.87	11.56	—	.46
Bipolar Affective Disorder	16.76	14.29	—	.60
Dysthymia	6.94	7.48	—	.86
Mood-stabilizer Medication	11.56	16.33	—	.28
Neuroleptic Medication	10.98	12.93	—	.86
Mean (SD) Data				
Age (y)	45.45 (15.05)	50.01 (13.57)	8.01[a]	<.01[c]
Disease Onset (age in y)	35.92 (16.05)	36.55 (14.38)	0.13[a]	.71
Previous Depressive episodes (n)	2.27 (4.83)	3.27 (7.59)	1.72[a]	.19
Duration of current episode (wk)	33.04 (56.40)	47.48 (67.95)	4.00[a]	.05
Pretreatment in current episode (wk)	17.73 (39.62)	24.05 (39.84)	1.37[a]	.24
Socioeconomic status (0–3)	1.56 (.08)	1.55 (.09)	<.01[a]	.92
Psychopathology				
Hamilton depression (HAM-D) score	28.32 (6.05)	26.39 (6.04)	8.11[b]	<.01[c]
HAM-D cognitive subscale	1.59 (.43)	1.53 (.42)	1.56[b]	.21
HAM-D vegetative subscale	2.27 (.67)	2.02 (.71)	12.11[b]	<.001[c]
HAM-D nonatypical subscale: 5 items	6.40 (2.49)	5.09 (2.61)	23.81[b]	<.00001[c]
HAM-D remaining items: 16 items	21.95 (4.96)	21.25 (4.92)	1.22[b]	.27

Parametric variables were analyzed by using the general linear model; nonparametric variables were analyzed by using Fisher's exact test.

BMI, body mass index.

[a]Degrees of freedom = 1,318.

[b]Degrees of freedom = 1,316.

[c]Statistically significant.

Attention

For neuropsychological examination, further preconditions (age <60 y, sufficient German language abilities, no history of head trauma or electroconvulsive therapy) were required. Three standard tests were conducted at admission and before discharge. Cognitive processing speed was assessed by using the Zahlenverbindungstest (ZVT; Oswald and Roth 1987), which is similar to the Trail Making Test. Processing time required for errorless performance was measured. The Aufmerksamkeits-Belastungstest (d2; Brickenkamp 2002) is a cancellation test that measures selective visual attention. Performance score is calculated by subtracting commission errors from correctly canceled items. Divided attention was assessed by means of a dual-task paradigm (visual and auditory stimuli) with the Testbatterie zur Aufmerksamkeitsprüfung (TAP; Zimmerman and Fimm 1993). Performance was scored as mean reaction time.

Combined Dexamethasone–Corticotropin-releasing Hormone Test

The combined dexamethasone (dex) – corticotropin-releasing hormone (CRH) test was administered within 10 days (on average, 6 d) after admission and within 10 days (on average, 5 d) before discharge, as described by Kunzel *et al.* (2003).

Statistical Analysis

For between-subjects comparisons of quantitative variables, we used the general linear model (GLM), with age and gender as covariates as well as age at onset and duration of the index episode, when appropriate. For the analysis of clinical response (repeated measures), we applied linear mixed-effects modeling with weekly HAM-D ratings as within-subjects factor and BMI group as fixed factor. Intercept was included as random effect, with variance components structure assumed for the variance/covariance matrix. Age, gender, age at onset, and duration of the index episode were considered as baseline covariates. For the analysis of dex–CRH test parameters and neuropsychological variables at admission, we applied a GLM with the corresponding HAM-D-scores and years of education as additional covariates, respectively. Change in neuropsychological and neuroendocrinologic parameters during therapy was evaluated by GLM, including the respective baseline values (on admission) as covariates. Weight change after 5 weeks of treatment was evaluated by GLM after correction for the relative numbers of medication with known weight-changing side effects, according to the suggestions by Zimmermann *et al.* (2003). The analyses of medication-based approaches were controlled for comedication with antipsychotics and mood stabilizers.

Results

Body Mass Index in Patients and Controls

Patients with MDD (n = 408) had a significantly higher BMI than did healthy controls (n = 1029; patients, 25.05 ± 4.3; controls, 24.42 ± 4.0) [$F(1,1434) = 7.84$, $p < .01$].

Psychopathology

The mean HAM-D score at admission was significantly lower in the high-BMI group. High-BMI patients displayed a significantly lower score in the HAM-D subscale vegetative depression (Overall and Rhoades 1982). We used the sum of five HAM-D items (loss of weight; insomnia early, middle, and late; and loss of appetite) indicating depressive symptoms, which are not