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ORIGINAL PAPER

Major depression, borderline personality disorder, and visceral fat content in women

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Abstract Major depressive disorder (MDD) is associated with increased volumes of visceral fat and a high prevalence of the metabolic syndrome. In turn, affective disorders are frequently found in patients with borderline personality disorder (BPD). It is therefore unclear whether BPD per se may influence body composition. In order to clarify a potential relationship between BPD and body composition, we measured visceral fat content (VFC) in young depressed women with and without comorbid BPD and related this parameter to various features of the metabolic syndrome. Visceral fat content was measured by magnetic resonance imaging in 22 premenopausal women with MDD only, in 44 women with comorbid MDD and BPD, in 12 female BPD patients without MDD, and in 34 healthy women (CG). Data showed that depressed women without comorbid BPD had a 335% higher VFC and women with comorbid BPD had a 250% higher VFC than the CG women. When controlling for age, data showed significant effects of MDD on VFC ($F = 8.4$; $P = 0.005$). However, BPD, with or without MDD, was not related to VFC. Young depressed women with and without comorbid BPD display increased visceral fat content when compared to control subjects and may therefore constitute a risk group for the development of the metabolic syndrome. BPD per se is not an additive risk factor in this context.

Keywords Visceral fat content · Body composition · Major depressive disorder · Borderline personality disorder · Metabolic syndrome · Cytokines

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Introduction

Patients with major depression show a doubling of the mortality rate at any age, independent of suicide. Sequelae of the metabolic syndrome are likely to play an important role, and the relative risk for coronary artery disease in patients with major depression is 1.5-fold to 2.0-fold in studies that controlled for risk factors such as smoking and physical activity [7, 20, 21, 24, 25, 34].

Impaired functioning of the hypothalamic–pituitary–adrenal axis (HPA axis) has been hypothesized to underlie this relationship. Depressed patients exhibit higher basal cortisol levels and nonsuppression of cortisol secretion after dexamethasone administration, providing an overall picture of impaired feedback and HPA axis overactivity [5, 39]. Hypercortisolemia itself is directly associated with an increased visceral fat content (VFC) as seen in Cushing's syndrome. Current evidence supports that the VFC is a major determinant of the metabolic syndrome [2, 3, 22, 23,

50]. Visceral fat is also an important organ to produce various cytokines, such as, leptin, IL-6, and TNF-alpha. Previous work has shown that glucose tolerance and insulin sensitivity are reduced in individuals with elevated circulating levels of these inflammatory biomarkers [1, 32]. Increased concentrations of proinflammatory cytokines were also observed in major depressive disorder (MDD) and constitute a possible link between MDD, altered body composition, and the metabolic syndrome [18, 28, 53].

The great majority of patients with MDD suffer from one or more other comorbid mental disorders [29]. About 30 to 80% of patients with MDD have a comorbid personality disorder, most frequently avoidant or BPD [36, 38]. In a reverse perspective, as many as 85% of patients with BPD will experience MDD at some point [15, 54]. Patients with borderline features are characterized by high levels of childhood adversity, a high level of functional impairment, and a high chronicity of the mental disorder [14]. An earlier study showed that patients suffering both diseases have a similar or higher visceral fat content compared to patients with depression only [18]. However, although BPD has been associated with increased rates of obesity and diabetes mellitus [11, 13], it is not known whether the development of the metabolic syndrome [4] is independently related to BPD. Psychosocial factors, poor health habits, and pathophysiological alterations in BPD might contribute to abdominal obesity and an increased metabolic risk profile.

As such, our study examined an extended sample of participants [18] to explore whether depression and BPD are independently associated with an increased visceral fat content (VFC) and to further explore the role of endocrine and metabolic covariates that are relevant in this context.

Participants and methods

Participants

Twelve women with BPD without lifetime depression, 22 women with major depressive disorder (MDD), and 44 women with MDD and comorbid BPD (MDD + BPD) were included. Diagnosis was made according to DSM-IV criteria and confirmed using a standardized clinical interview (SCID I/II; German version) by trained and supervised clinicians. Exclusion criteria comprised a body mass index (BMI) $\leq$ 17.5 kg/m^2, schizophrenia, mental retardation, alcohol or drug abuse, diabetes mellitus, inflammatory or infectious disease, cardiovascular disease, pregnancy, and an age below 18 years. A total of 67 patients received psychotropic medication (18 women received neuroleptics, 16 women received tricyclic antidepressants, and 41 women received selective serotonin reuptake inhibitors). Thirty-four healthy women served as a comparator group (CG). A standardized psychiatric interview provided no evidence of either an individual or a family history of major psychiatric disorders in any subject within this group. None of the comparator subjects suffered from an acute or chronic illness or took any medication. The study was approved by the local ethics committee, and all subjects gave their written informed consent.

Study design

Visceral fat content was quantified by magnetic resonance imaging. After carrying out a scout scan, visceral fat was measured in all subjects at the level of the first lumbar vertebral body. Additional scans were performed 10 mm above and below L4 to gain more detailed information about the distribution of fat tissue. Mean sum scores for the 3 levels were analyzed for each group. The areas (mm^2) of fat were calculated on the basis of the total number of pixels of fat density (−70/−150 signal intensity units) within the anatomic compartments delineated using a graph pen. The two independent raters were blind to the diagnostic status of the subjects. The visceral fat area at the L4 level is highly correlated with total visceral fat volume ($r = 0.95$ as reported by Ross et al.) [35]. In women, visceral fat is higher correlated with cardiovascular risk factors and criteria of the metabolic syndrome than BMI or anthropometric indexes [26].

Assays

Fasting serum and plasma samples were collected between 07:00 and 08:00 am and stored at −80°C until analyses. Concentrations of fasting cortisol, insulin, and glucose were determined using well-established immunoassays and enzymatic methods (DPC, Los Angeles, USA and Nichols Institute Diagnostics, Bad Vilbel, Germany, Glucose Hexokinase). Concentrations of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) were assessed using high sensitivity ELISA kits (HS Quantikinine; R&D systems, Wiesbaden, Germany). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting glucose and insulin concentration divided by 22.5, while the quantitative insulin sensitivity check index (QUICKI) was calculated as the reciprocal of the log of the product of fasting insulin and glucose concentrations [19].

Statistical analyses

Data are reported as mean values ± standard deviation (SD). One-way analysis of variance was used to compare data by diagnosis (MDD; BPD). Relationships between

visceral fat depot and independent variables were assessed by simple linear regression to estimate the strength of association between individual risk factors and visceral fat. Multivariate regression analysis was performed to determine the associations between covariates and visceral fat content. In this subsequent analysis, all predictors that were significant after simple regression analysis as well as presence of BPD were chosen for testing in a forward step-wise selection algorithm. The model was tested for multicollinearity using variance inflation factors. Data that followed a skewed distribution (VFC, Glucose, Insulin, HOMA-IR, IL-6, TNF-alpha) were transformed logarithmically. A P value below 0.05 was considered to be significant. Data were analyzed using SPSS (version 17.0).

Results

Women with MDD either with or without comorbid BPD had a similar VFC after adjusting for age. These two patient groups had higher VFC than women with BPD alone or healthy controls (Fig. 1). Depressed women without comorbid BPD had a 335% larger VFC than the CG (6,251 ± 6,243 vs. 1,434 ± 5,907 mm^2), while women with comorbid BPD showed a 250% higher VFC (5,010 ± 5,817 vs. 1,434 ± 5,907 mm^2). Women with BPD without a lifetime diagnosis of MDD showed no substantial differences in the amount of VF when compared to CG. ANCOVA with age as a covariate revealed significantly higher VFC with MDD (df = 1; $F = 8.4$; $P = 0.005$). Both the factor BPD (df = 1; $F = 0.03$; $P = 0.86$) and the interaction term BPD * MDD (df = 1; $F = 0.65$; $P = 0.42$) were not significant.

Table 1 shows that study groups were similar with respect to height, body weight, and BMI. Higher concentrations of fasting glucose were observed in women with a diagnosis of MDD ($F = 10.6$; $P = 0.002$). BPD was associated with higher levels of fasting insulin ($F = 4.6$, $P = 0.04$) and elevated HOMA-IR ($F = 4.8$; $P = 0.03$). Furthermore, higher concentrations of TNF-alpha were observed for MDD ($F = 56.2$; $P < 0.001$) and to a somewhat lesser extent for MDD comorbid with BPD ($F = 5.8$, $P = 0.018$). No significant differences were observed for IL-6 or cortisol.

Simple regression analysis with the dependent variable VFC showed significant relationships with age ($\beta = 0.254$; $P = 0.007$), BMI ($\beta = 0.589$; $P < 0.001$), fasting insulin ($\beta = 0.319$; $P = 0.001$), HOMA-IR ($\beta = 0.318$; $P = 0.001$), QUICKI ($\beta = -0.304$; $P = 0.001$), TNF-alpha ($\beta = 0.227$; $P = 0.037$), Beck Depression Inventory ($\beta = 0.315$; $P = 0.001$), and MDD ($\beta = 0.39$; $P < 0.001$) (Fig. 2). Fasting glucose, fasting cortisol, IL-6, BPD, neuroleptic drug use, use of tricyclic antidepressants, or use of selective serotonin reuptake inhibitors were not significantly related to visceral fat stores.

In a multiple linear regression analysis, a model consisting of age, BMI, fasting insulin, HOMA-IR, QUICKI, TNF-alpha, Beck Depression Inventory, BPD, and MDD explained 38.8% of the variance in VFC. Independent significant predictors for VFC were age ($r = 0.24$; $P = 0.013$), BMI ($r = 0.43$; $P < 0.001$), and MDD ($r = 0.25$; $P = 0.008$).

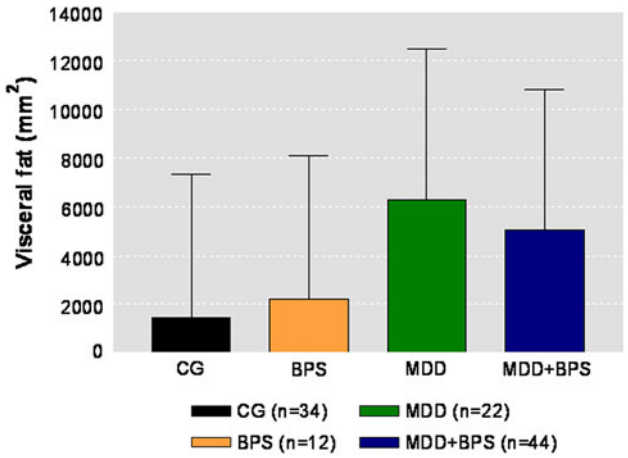

Fig. 1 Analysis of variance with age as a covariate revealed significantly higher visceral fat content with MDD (df = 1; $F = 8.4$; $P = 0.005$). The factor BPD (df = 1; $F = 0.03$; $P = 0.86$) and the interaction term BPD *MDD (df = 1; $F = 0.65$; $P = 0.42$) were not significant. *CG* control group, *MDD* major depressive disorder, *BPD* borderline personality disorder

Discussion

In this study, we provide evidence that the high VFC volumes found in patients with MDD and BPD must be attributed to the depression component of the disorder. Various cross-sectional studies examined the association between depressive symptoms, MDD, and VFC. For incidence, Everson-Rose et al. observed that middle-aged overweight and obese women with CES-D scores ≥16 had significantly more visceral fat than women with few depressive symptoms even after adjusting for physical activity [9]. One longitudinal study among older persons found that high baseline depressive symptoms resulted in a greater increase in visceral fat over 5 years. These results remained significant even after adjusting for sociodemographics, overall obesity, lifestyle, and antidepressive medication [49]. Studies among patients with MDD showed comparable results [8, 9, 45, 50, 52]. These data provide evidence for underlying pathways associated with the disorder per se and not with health habits or medication

Table 1 Basal data, endocrine measures and proinflammatory cytokines in patients, and healthy subjects (mean ± standard deviation)

	CG ($n = 34$)	BPD ($n = 12$)	MDD ($n = 22$)	MDD + BPD ($n = 44$)	Analysis of variance
Age (y)	28.1 ± 6.9	26.8 ± 5.0	36.9 ± 8.4	30.0 ± 7.9	MDD (df = 1; $F = 14.3$; $P < 0.001$)
					BPD (df = 1; $F = 6.6$; $P = 0.012$)
Height (m)	1.69 ± 0.05	1.68 ± 0.06	1.67 ± 0.05	1.68 ± 0.07	NS
Weight (kg)	65.6 ± 11.4	66.8 ± 11.0	69.3 ± 12.5	66.7 ± 13.4	NS
BMI	22.9 ± 3.7	23.7 ± 3.8	25.1 ± 5.4	23.6 ± 4.6	NS
Fasting glucose (mmol/l)	4.5 ± 0.6	4.6 ± 0.4	4.8 ± 0.3	4.9 ± 0.5	MDD (df = 1; $F = 10.6$; $P = 0.002$)
Cortisol (nmol/l)	554 ± 118	599 ± 181	627 ± 339	640 ± 196	NS
Fasting insulin (mU/l)	6.7 ± 3.4	8.6 ± 4.7	7.9 ± 4.4	10.3 ± 5.6	BPD (df = 1; $F = 4.6$; $P = 0.035$)
HOMA-IR	1.4 ± 0.8	1.8 ± 1.0	1.7 ± 0.9	2.3 ± 1.3	BPD ((df = 1; $F = 4.8$; $P = 0.031$)
QUICKI	0.375 ± 0.03	0.360 ± 0.03	0.363 ± 0.03	0.351 ± 0.04	NS
IL-6 (pg/ml)	0.9 ± 0.6	1.3 ± 0.9	1.3 ± 1.7	1.5 ± 1.3	NS
TNF-alpha (pg/ml)	1.8 ± 0.6	2.0 ± 0.8	4.0 ± 0.9	2.9 ± 1.2	MDD (df = 1; $F = 56.2$; $P < 0.001$)
					BPD (df = 1; $F = 5.8$; $P = 0.018$)
					MDD*BPD (df = 1; $F = 9.3$; $P = 0.003$)
Beck Depression Inventory (points)	0.7 ± 1.1	13.5 ± 5.2	32.5 ± 8.2	24.2 ± 7.8	MDD (df = 1; $F = 292.6$; $P < 0.001$)
					BPD (df = 1; $F = 15.1$; $P < 0.001$)
					MDD*BPD (df = 1; $F = 86.8$; $P < 0.001$)

CG control group, *MDD* major depressive disorder, *BPD* borderline personality disorder

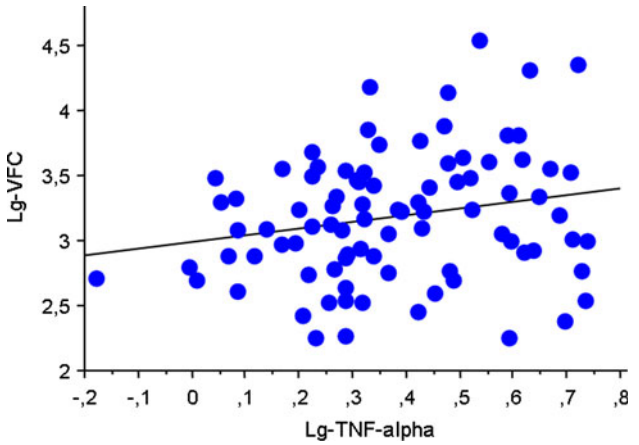

Fig. 2 Simple regression analysis with VFC as the dependent and TNF-alpha as the independent variable ($\beta = 0.227$; $P = 0.037$). *VFC* visceral fat content

alone. Despite this, issues relating to psychiatric comorbidity, disease severity, and the role of childhoods antecedents of mental disorders have not yet been sufficiently addressed.

BPD and childhood maltreatment are associated with an increased risk for obesity, ischemic heart disease, diabetes mellitus, and stroke [6, 10, 12, 37]. However, from these studies it remains unclear whether this is mediated by BPD alone or by comorbid conditions. Although BPD had no significant influence on VFC in our sample, we found hyperinsulinemia and higher HOMA-IR in women with BPD only. Hyperinsulinemia may indicate disturbed glucose allocation due to the attenuated HPA and sympathetic nervous system in our patients with BPD [33]. Over a longer period of time, hyperinsulinemia may contribute to a higher risk of weight gain and diabetes mellitus [31, 41]. The observed high-normal HOMA-IR in BPD indicates an increased risk for impaired glucose tolerance in this patient group. The underlying mechanism that determine the increased metabolic risk is yet not identified. The interactions between health behavior, high psychiatric comorbidity, and neuroendocrine and metabolic alterations in BPD are complex.

Depressed patients in our sample showed further metabolic risk factors independent of comorbidity with BPD. In patients with MDD, higher fasting glucose concentrations were observed than was the case in healthy controls. Altered glucose metabolism in MDD has been demonstrated elsewhere using oral glucose tolerance tests [51] and the glucose clamp technique [40]. Several studies have demonstrated that high-normal blood glucose concentrations are associated with an increased risk for diabetes [30, 46].

Another important finding was the increased serum concentrations of TNF-alpha in MDD and its association with VFC. TNF-alpha has been proposed as an important link between altered body composition and the metabolic syndrome. In a cross-sectional population-based study, TNF-alpha but not IL-6 remained significantly associated with the metabolic syndrome after adjusting for multiple

confounders [43]. In contrast to IL-6, TNF-alpha is secreted not by adipocytes but instead by infiltrating macrophages and acts through autocrine and paracrine mechanisms. Particularly in experimental studies, TNF-alpha impairs peripheral glucose uptake and metabolism by altering insulin signaling [27, 42]. TNF-alpha might be one possible factor explaining the observed metabolic risk profile in our depressed patients. Contrary to our expectations, patients with both BPD and MDD had lower TNF-alpha concentrations than patients with MDD alone. Further studies should focus on the effects of psychiatric comorbidity and the consequences for inflammatory pathways.

We found no significant increase in cortisol concentrations in all patient groups. Furthermore, no association between cortisol concentration and VFC was found. At first glance, this might be surprising due to the fact that hypercortisolism is suggested to be the origin of abdominal obesity (e.g. in Cushing's syndrome). Cortisol in the presence of insulin stimulates lipid uptake by activating lipoprotein lipase, an effect that is facilitated by high concentrations of the cortisol-activating enzyme 11-β-hydroxysteroid dehydrogenase type I and glucocorticoid receptors in intra-abdominal fat [48]. But first of all, single cortisol measurement as done in our study does not reliably reflect the status of the HPA axis. In most patients with depressive disorders, no excessive increase in cortisol but altered cortisol patterning was found [5]. A second explanation might be that the antidepressant use in our patients resulted in a reverse of the HPA alterations as shown in several studies [16, 17]. Third, the status of the HPA axis might differ dependent on comorbid conditions. For example, patients with adverse childhood experiences might exhibit hypocortisolemia even if they are not diagnosed with posttraumatic stress disorder [44, 47]. This data point to the relevance of focussing on comorbid conditions as well as adverse childhood experiences.

The cross-sectional nature of the study and the restricted number of participants both represented limitations in our study design. Our study had a power higher than 80% to detect the differences in VFC between the comparator group and the MDD group, as well as between the comparator group and the comorbid BPD group. The power for detecting smaller differences—such as the one between the comparator group and the BPD only group, and the one between the MDD and the comorbid BPD group—was low. Furthermore, we studied only premenopausal women; thus, our findings cannot be generalized to men and elderly patients. Attention should also be paid to the fact that single measurement of fasting insulin, glucose, and cortisol only allows to estimate glucose tolerance, insulin resistance, and status of the HPA axis.

In summary, we have shown that a lifetime diagnosis of MDD is associated with a higher VFC in young and normal weight women. BPD was not associated with any additional effects on VFC. In both patient groups, additional metabolic alterations were observed indicating a higher risk for developing obesity, diabetes mellitus, and cardiovascular disease.

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Conflict of interest None of the authors reported potential conflicts of interest.

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