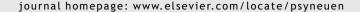


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# Do depressed patients without activation of the hypothalamus—pituitary—adrenal (HPA) system have metabolic disturbances?



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### **KEYWORDS**

Depression; Metabolic syndrome; HPA system; Autonomic nervous system; Blood pressure; Fasting glucose; Body composition; Visceral fat Summary This study compared features of the metabolic syndrome between healthy controls and depressed patients without activation of the hypothalamus—pituitary—adrenal (HPA) system. After exclusion of non-suppressors to 1 mg dexamethasone, we included 20 depressed inpatients and 34 healthy controls in the analyses. We assessed HPA system activity (diurnal saliva cortisol profile, cortisol excretion), normetanephrine excretion as well as fasting glucose, lipid profile and blood pressure. With regard to body composition, we measured waist circumference as well as visceral fat and adrenal volume by magnetic resonance (MR) imaging. Five depressed patients (25%) and five healthy controls (15%) fulfilled the criteria of the metabolic syndrome according NCEP-ATP-III. Depression was significantly related with fasting glucose and negatively associated with mean blood pressure (BP) and, by trend, with low HDL-cholesterol. We conclude that depressed patients may have modest metabolic disturbances even in the complete absence of

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activation of stress-responsive systems. Hence some metabolic disturbances in depressed patients may not be explicable by HPA activation. Additional factors are required to mediate the link between affective and metabolic disorders.

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### 1. Introduction

It has been recognized for almost three decades that depressed patients suffer a substantially increased risk for metabolic syndrome (Kinder et al., 2004), diabetes mellitus type 2 (Wannamethee et al., 2005) and insulin resistance (Kan et al., 2013) as well as coronary artery disease (Rugulies, 2002). Based on Björntorp's groundbreaking observation that stress and cortisol may cause abdominal obesity and the metabolic syndrome (Björntorp, 2001), psychiatric research began to investigate the hypothesis that activation of the hypothalamus-pituitary-adrenal (HPA) system during depression may lead to secondary metabolic disorders. In fact, it has been shown in epidemiological studies that the impact of depression on the development of the metabolic syndrome may be, at least partially, mediated by cortisol (Vogelzangs et al., 2007). Moreover, studies in clinical samples found a positive relation between HPA system activity and visceral obesity (Weber-Hamann et al., 2002) as well as insulin resistance (Weber-Hamann et al., 2005). Thus, activation of the HPA system may explain some, but not all features of the metabolic syndrome in depressed patients.

In addition to metabolic disturbances, body composition may differ between healthy controls and depressed patients, not only with regard to the well-known effects of depression on visceral obesity (Weber-Hamann et al., 2002) or bone mineral density (Schweiger et al., 1994). Adrenal volume has been found increased in depressed patients in several studies, which indicates that adrenal volume may reflect long-term ACTH overdrive leading to hyperplasia in this clinical population (Kessing et al., 2011). Thus, increased visceral fat and adrenal volume can be considered proven morphological adaptations to chronic stress and hypercortisolemia in depression.

However, not all depressed patients show signs of stress system activation. Interestingly, several studies failed to demonstrate increased HPA system activity in depressed outpatients (Strickland et al., 2002; Peeters et al., 2004; Van Den Eede et al., 2006; Carpenter et al., 2009). Also, the clinical subtype may play a role with melancholic and atypical depression displaying different features of HPA regulation (Gold and Chrousos, 2002). Accordingly HPA activity was concluded to vary strongly between patient groups with pronounced HPA activation in depression with melancholic or psychotic features as well as in elderly patients (Stetler and Miller, 2011), but not in patients with atypical depression, less severe depression or depressed outpatients (O'Keane et al., 2012).

On grounds of these observations one may wonder whether depressed patients without evidence for increased HPA system activity may in fact be precluded from metabolic risks. This hypothesis, to the best of our knowledge, has never been tested. In contrast, previous studies on metabolic disturbances in depressed patients by our group and others rather aimed at melancholic and hypercortisolemic

depressed patients (Schweiger et al., 1994; Weber-Hamann et al., 2002, 2005; Kessing et al., 2011). Therefore, our study intended to compare symptoms of the metabolic syndrome and body fat distribution between healthy controls and moderately depressed patients without activation of stress-responsive systems as defined by a negative dexamethasone suppression test.

#### 2. Methods

#### 2.1. Subjects

#### 2.1.1. Ethical aspects

The trial was registered at the German Clinical Trial Registry (DRKS00004324), was approved by the local ethics committee and all subjects gave signed informed consent. The study was conducted with inpatients at a university psychiatric hospital in Germany. Healthy controls were recruited via ads in local newspapers.

#### 2.1.2. Inclusion/exclusion criteria

Inclusion criteria for patients were (1) major depression according DSM-IV criteria, (2) a score of at least 18 points on the 21-item Hamilton Depression Rating Scale (HDRS), (3) no history of substance abuse or dependency (except nicotine), (4) absence of neurological or relevant medical disorders and (5) body mass index (BMI) below 35 kg/m<sup>2</sup>, (5) no dieting or medication for hypertension, dyslipidemia, diabetes mellitus, (6) suppression of morning cortisol after nighttime dexamethasone (morning cortisol <5  $\mu$ g/dl after 1.0 mg dexamethasone at 11 p.m.), (7) no pre-treatment with fluoxetine or longacting injectable antipsychotics. The criteria (3)–(7) were also applied for healthy controls and none of the healthy controls was treated with any psychopharmacological drug. Significant psychiatric or somatic diseases were excluded by a detailed history, psychiatric interview (SCIDI), physical examination and routine laboratory tests. Healthy volunteers underwent the same study procedures as patients at baseline, but were not hospitalized.

#### 2.1.3. Healthy controls

We excluded three subjects (controls only) from the analysis since post-dexamethasone cortisol more than 5 SDs above mean and interview indicated that dexamethasone was most likely not ingested. Finally, we selected 34 healthy volunteers who were matched to participating patients with respect to age and BMI.

## 2.1.4. Depressed patients

We excluded subjects with dexamethasone suppression test (DST) nonsuppression and found no evidence for HPA system activation in our group of patients when considering DST, saliva cortisol, cortisol excretion in urine or adrenal volume (see Table 1). After exclusion of DST nonsuppressors, we

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