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Pericardial adipose tissue and the metabolic syndrome is increased in patients with chronic major depressive disorder compared to acute depression and controls

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ABSTRACT

Objective: Major depressive disorder (MDD) is associated with an estimated fourfold risk for premature death, largely attributed to cardiovascular disorders. Pericardial adipose tissue (PAT), a fat compartment surrounding the heart, has been implicated in the development of coronary artery disease. An unanswered question is whether people with chronic MDD are more likely to have elevated PAT volumes versus acute MDD and controls (CTRL).

Methods: The study group consists of sixteen patients with chronic MDD, thirty-four patients with acute MDD, and twenty-five CTRL. PAT and adrenal gland volume were measured by magnetic resonance tomography. Additional measures comprised factors of the metabolic syndrome, cortisol, relative insulin resistance, and pro-inflammatory cytokines (interleukin-6; IL-6 and tumor necrosis factor-α, TNF-α).

Results: PAT volumes were significantly increased in patients with chronic MDD > patients with acute MDD > CTRL. Adrenal gland volume was slightly enlarged in patients with chronic MDD > acute MDD > CTRL, although this difference failed to reach significance. The PAT volume was correlated with adrenal gland volume, and cortisol concentrations were correlated with depression severity, measured by BDI-2 and MADRS. Group differences were found concerning the rate of the metabolic syndrome, being most frequent in chronic MDD > acute MDD > CTRL. Further findings comprised increased fasting cortisol, increased TNF-α concentration, and decreased physical activity level in MDD compared to CTRL.

Conclusion: Our results extend the existing literature in demonstrating that patients with chronic MDD have the highest risk for developing cardiovascular disorders, indicated by the highest PAT volume and prevalence of metabolic syndrome. The correlation of PAT with adrenal gland volume underscores the role of the hypothalamus-pituitary-adrenal system as mediator for body-composition changes. Metabolic monitoring, health advices and motivation for the improvement of physical fitness may be recommended in depressed patients, in particular in chronic depression.

1. Introduction

Chronic major depressive disorder (MDD) is defined as a major depressive episode without remission for at least two years. Chronic MDD is common, with a lifetime prevalence of ~5% in the general population; around 20–30% of acutely depressed individuals typically go on to develop a chronic disease course (Gilmer et al., 2005; Kerling et al., 2016). Chronic MDD is distinguished from acute MDD by an earlier onset (Gilmer et al., 2005), increased comorbidity with axis 1 disorders (Gilmer et al., 2005; Keller et al., 1998; Mondimore, 2005), higher rates of personality disorders (Garyfallos et al., 1999), higher rates of childhood trauma (Klein et al., 2015), greater suicidality (Garvey et al., 1986) and functional impairment (Gilmer et al., 2005; Hays et al., 1995), higher rates of mood disorders in relatives (Mondimore et al.,

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2006; Klein et al., 2004), and worse treatment outcome (Kocsis, 2003; Gelenberg et al., 2006; Mcgrath et al., 2006). Chronic MDD is associated with significant individual and societal costs, documented by higher unemployment rates and lower rates of marriages across this patient group (Angst et al., 2009).

The comorbidity of acute MDD with coronary artery disease (CAD) is common, and has also been observed in patients with chronic MDD (Angst et al., 2009). Depression and coronary artery disease are considered to have a bidirectional relationship. Recent studies examining depression as a risk factor for developing CAD have found increased rates of incident cardiovascular disease (Rugulies, 2002) and ischemic heart disease mortality (Surtees et al., 2008). The underlying mechanisms that link MDD with cardio-metabolic disorders are complex. Key factors contributing include the increased rate of the metabolic syndrome in MDD (Vancampfort et al., 2014), increased rates of type-2 diabetes mellitus (Mezuk et al., 2008; Stubbs et al., 2015), increased intra-abdominal adipose tissue (Weber-Hamann et al., 2006), dysregulation of the hypothalamus-pituitary-adrenal axis (HPAS) with subsequent alterations in cortisol concentrations (Burke et al., 2005), dysregulation of pro- and anti-inflammatory cytokines (Dowlati et al., 2010), and poor lifestyle habits (e.g. smoking, physical activity, dietary factors) (Kerling et al., 2016; Blumenthal, 2013; Moselhy et al., 2012).

Recently, increased pericardial adipose tissue (PAT) has been observed in patients with acute MDD (Kahl et al., 2014). PAT is a fat deposit surrounding the heart, with close anatomic proximity to coronary arteries. Research from the general population has shown that similarly to intra-abdominal adipose tissue, PAT secretes pro-inflammatory cytokines that may be implicated in early-stage CAD (Miao et al.). PAT is strongly associated with myocardial ischemia and coronary heart disease, even after adjusting for body mass index (Locke et al., 2015) and other cardiovascular risk factors (Ding et al., 2009; Kim et al., 2011). The results of general population-based studies have demonstrated that PAT is positively correlated with coronary artery calcification (Ding et al., 2008), inflammatory markers, and carotid intima-media thickness (Tadros et al., 2010; Soliman et al., 2010).

To the best of our knowledge, to date, no study has investigated if PAT volume differs among people with chronic MDD compared to those with acute MDD or controls. Therefore, our primary aim was to examine PAT volumes in patients with chronic MDD by cardiac magnetic resonance imaging (Tsimring et al., 2005), and to relate PAT volumes to adrenal gland volumes, a proxy parameter for HPAS activation. Our main hypothesis was that chronic MDD is associated with higher PAT volumes and worse metabolic parameters compared to patients with acute MDD and healthy controls.

2. Methods

2.1. Study procedure and eligibility criteria

The recruitment process, including the eligibility criteria are described in details elsewhere (Kahl et al., 2014). In short, all patients were recruited after written informed consent at the Department of Psychiatry, Social Psychiatry and Psychotherapy of Hannover Medical School, and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) criteria, confirmed by standardized clinical interviews (SCID I/II; German version).

Exclusion criteria included comprised acute or chronic infectious disease, lifetime immune or autoimmune disorders, type-2 diabetes mellitus, lifetime or current cardiovascular disease, pregnancy, schizophrenia, mental retardation, bipolar disorder, current substance abuse age younger than 18 and older than 60 years (Kahl et al., 2014).

2.1.1. Participants

The current study utilizes data from an ongoing study including two groups of people with depression. First, adults with acute MDD (N = 34) were defined as those with a major depressive episode, defined as major depression with a duration less than two years, and no comorbidity with dysthymic disorder (N = 34). Second, the chronic MDD group ($N = 16$) was defined as those with MDD with comorbid dysthymic disorder, or MDD with a duration longer than two years, or MDD with partial response but still fulfilling MDD criteria (Kahl et al., 2014). All patients were treated with psychotherapy, and 40/50 patients received psychopharmacological drugs. In particular, 16 patients were treated with selective serotonine reuptake inhibitors, 11 with agomelatine, nine with dopamine and noradrenaline reuptake inhibitors, eight with selective serotonine and noradrenaline reuptake inhibitors, three with quetiapine, and one patient received lithium. Eight of sixteen patients in the chronic MDD group reported an onset of the disorder before the age of 20 y, compared to seven of thirty-four patients in the acute depression group.

Twenty-five healthy subjects (CTRL) were recruited through announcements on university bulletin boards. Potential control subjects with mental and physical disorders were excluded, determined by using a standardized psychiatric interview and a physical examination.

2.1.2. Behavioral assessments

Depression severity was assessed using the German versions of the 10-item, clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) and the self-reported, 21-item Beck Depression Inventory (Aad et al., 2015). Physical activity was assessed using a 6-point Likert scale with descriptors ranging from “never” (Gilmer et al., 2005) to “very often” (Cuppett and Latin, 2002). Smoking habits were measured in pack-years (the number of cigarettes smoked per day × years of smoking/20), and alcohol consumption was measured in drinks consumed per week.

2.1.3. Magnetic resonance imaging

Pericardial adipose tissue (PAT) and adrenal gland volume were examined using a 1.5 Tesla MRI scanner (Avanto, Siemens Healthcare) (Sacks and Fain, 2011). To quantify PAT, ECG-gated T1-weighted dark-blood turbo spin-echo sequences were acquired in short- and long-axis views at the following specifications: TR/TE = 750/37 ms, flip angle = 180°, matrix = 384 × 187, field of view = 380 mm, and slice thickness = 10 mm. PAT was quantified between the atrioventricular plane and the apex by segmentation using QMass 7.1 software (Medis, Leiden, The Netherlands).

Adrenal gland volumes were determined using a VIBE Dixon sequence with 2 mm slice thickness and QMass 7.1 software (Medis, Leiden, The Netherlands) by manual segmentation. To obtain the intra-observer variability the manual segmentation of the adrenal glands was done twice. Volumes of right and left adrenal gland were added, and expressed as total adrenal gland volume.

All measurements were performed by raters blinded for the status of study participants.

2.1.4. Blood sampling

Fasting serum samples were collected between 0700 h and 0800 h and stored at −80 °C until the analysis. Concentrations of fasting glucose and fasting cortisol were determined with established immunoassays (Roche Diagnostics, Mannheim, Baden-Württemberg, Germany). Concentrations of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were determined using high sensitivity ELISA kits according to the manufacturer's instructions (HS Quantikinine; R&D Systems, Wiesbaden, Germany). Relative insulin resistance was determined using the homeostasis assessment model (Matthews et al., 1985).

2.1.5. StatistIcal analysis

Data were analyzed using IBM SPSS Statistics (version 23). Group differences concerning PAT were determined utilizing ANCOVA. Since it was previously demonstrated that gender and age make an essential contribution to the amount of cardiac adipose tissue, we used group and gender as independent variables, PAT as dependent variable, and