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Reduced muscle mass in middle-aged depressed patients is associated with male gender and chronicity

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ABSTRACT

Objective: Reduced muscle mass is a characteristic finding in sarcopenia, the central element of physical frailty syndrome, and a major cause of physical function decay, morbidity and mortality in the elderly. Studies so far demonstrated reduced muscle mass in depressed patients with an average age over 60 years. An open question is whether muscle mass reduction is already observed earlier. Therefore, muscle mass was assessed in middle-aged male and female depressive patients, and the findings were related to indicators of hypothalamus-pituitary adrenal axis activation, lifestyle factors, endocrine and immune measures.
Methods: Sixty-seven depressed patients (mean age 38.6y; 58.2% female) and 26 healthy volunteers (mean age 40.5y; 61.5% female) were included. Muscle mass, adrenal gland volume, and intra-abdominal adipose tissue were assessed by magnetic resonance tomography. Laboratory parameters included fasting cortisol, pro-inflammatory cytokines, factors constituting the metabolic syndrome, and relative insulin resistance according to the homeostasis model assessment (HOMA-IR).
Results: We found significant effects of depression ($F = 4.2$; $P = 0.043$) and gender ($F = 182$; $P < 0.001$) on muscle mass. Muscle mass was reduced in depressed men compared to healthy men ($F = 3.4$; $P = 0.044$), particularly in those with chronic depression. In contrast, no such association was observed in depressed females. Adrenal gland volume and intra-abdominal fat was increased in depressed men and women, although not significantly. Correlations were observed for muscle mass with the amount of self-reported exercise and depression severity, and for depression severity with self-reported exercise. Further findings comprised lower self-reported activity and higher cortisol concentrations in depressed male and female compared to healthy probands.
Conclusions: Muscle mass is reduced in middle-aged depressed men, particularly those with chronic disease course. This association is not observed in depressed females, possibly pointing to the role of female sex steroids in maintaining muscle mass. The increase of adrenal gland volume in depressed patients may point to the role of a dysregulated hypothalamus-pituitary-adrenal system. The inverse association of exercise with muscle mass demonstrates the importance of physical activity. Looking at the long term consequences of reduced muscle mass, interventions to preserve and rebuild muscle mass in depression – such as structured exercise interventions – should be recommended.
Significant outcomes: Muscle mass is decreased in male patients with major depressive disorder, particular those with chronic disease course. This difference was not observed in female depressed patients. The extent of muscle mass reduction is correlated to depression severity and inversely to physical activity, pointing to the role of depression associated inactivity. Low muscle mass is a risk factor for physical frailty, therefore interventions aiming at improving physical fitness may be recommended.
Limitations: Sex steroids were not assessed in the study groups.

1. Introduction

Body-composition changes have frequently been observed in middle-aged patients with major depression, including increased volumes of intra-abdominal adipose tissue, increased pericardial adipose

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tissue, and decreased bone mass. Body-composition changes are risk factors for the development of frequent physical disorders such as type-2 diabetes mellitus (increased intra-abdominal adipose tissue) (Bjorntorp and Rosmond, 1999), osteoporotic fractures (reduced bone mineral density) (Whooley et al., 1999), and cardiovascular disorders (increased pericardial fat) (Liu et al., 2010), and all of the aforementioned diseases are more prevalent in patients with major depression (Mezuk et al., 2008; Van et al., 2007; Cizza et al., 2010; Schweiger et al., 2016; Vancampfort et al., 2015; Vancampfort et al., 2016a).

Another facet of body-composition refers to the muscle compartment. Peak muscle mass and muscle strength are attained in late adolescence/early adulthood, followed by an estimated 1–2% loss of muscle mass after the age of 35 years (Hughes et al., 2002). A progressive deterioration in muscle mass, strength and function fosters the development of sarcopenia (Rosenberg, 2011), the biological substrate of physical frailty (Landi et al., 2015). Sarcopenia is seen as the driver of decreased independence and quality of life in the elderly (Janssen et al., 2002), and conveys an increased risk of incident disability and all-cause mortality (Landi et al., 2016). Therefore, identification of antecedents and risk factors for sarcopenia/frailty are of public health importance. Major depressive disorder (MDD) may be such an antecedent due to the frequently observed alterations in lifestyle behaviors (e.g. decreased physical activity, decreased physical fitness, increased sedentary behavior) (Stubbs et al., 2016a; Schuch et al., 2016a; Kerling et al., 2016), and alterations in inflammatory (increase in pro-inflammatory cytokines) (Dowlati et al., 2010) and endocrine factors (hypercortisolism) (Carroll et al., 2012), that have all been associated with the development of frailty (Liu et al., 2016; Tak et al., 2013; Soysal et al., 2016). A recent systematic review concerning depression and frailty point to the prospective relationship between depressive symptoms and incident frailty (Vaughan et al., 2015).

However, few studies addressed the relationship between muscle mass and major depression. Kim and colleagues observed decreased muscle mass in depressed Korean men (mean age 71.3 years) (Kim et al., 2011), and Remigio-Baker and colleagues found lower muscle mass in depressed participants associated with male gender and Chinese origin (mean age 62.9 years) (Remigio-Baker et al., 2015). In the study by Wu et al. in 1046 Chinese participants (mean age 68.9 years), an inverse association between self-rated depressive symptoms, muscle mass and muscle strength was observed in both genders, although more pronounced in depressed men (Wu et al., 2016). In a recent epidemiological study by Byeon and colleagues using data from the Korean National Health and Nutrition Examination Survey (KNHANES), no association was found between sarcopenia and self-reported depressive symptoms (Byeon et al., 2016). All of the reported studies used self-rating instruments for the assessment of depressive symptoms, and only one comprised middle-aged depressed patients (Byeon et al., 2016). Furthermore, other body-composition compartments such as intra-abdominal fat were not reported in these studies. Therefore, we systematically assessed muscle mass, intra-abdominal fat and adrenal gland volume, a proxy parameter for the activity of the hypothalamus-pituitary adrenal axis (Kahl et al., 2015), in middle-aged patients with confirmed MDD diagnosis. Our primary hypothesis was a lower muscle mass in depressed patients compared to healthy controls.

2. Methods

2.1. Participants

Sixty-seven inpatients with MDD were recruited after informed written consent at the Department of Psychiatry of Hannover Medical School. The inclusion criteria were a diagnosis of major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Diagnosis was confirmed using standardized clinical interviews (SCID I/II; German version).

Chronic MDD was defined as those patients with MDD plus comorbid dysthymic disorder, or MDD with longer than two year duration, or MDD with partial response but still fulfilling MDD criteria. Exclusion criteria concerning psychiatric disorders were schizophrenia, bipolar disorder, current substance use disorder, and mental retardation.

At the time of the study, eighteen patients were treated with selective serotonin reuptake inhibitors, 16 with agomelatine, 11 with dopamine and noradrenaline reuptake inhibitors, 10 with selective serotonin and noradrenaline reuptake inhibitors, 4 with vortioxetine, 4 with quetiapine, 2 with mirtazapine, 2 with pregabaline, 2 with pregabaline, 1 with lithium, 1 with olanzapine, 1 with tricyclic antidepressants, and 2 with adjuvant benzodiazepines.

Twenty-six healthy subjects were recruited through announcements on university bulletin boards and served as comparison group (CTRL). A standardized psychiatric interview was applied to confirm the absence of any current or lifetime history of major psychiatric disorder for every subject in this group.

An exhaustive medical examination was performed in both groups. Exclusion criteria concerning physical disease for both groups were acute or chronic infectious disease, type-2 diabetes mellitus, lifetime or current cardiovascular disease, immune or autoimmune disease. Furthermore, exclusion criteria for both groups were an age younger than 18 years or older than 60 years, and pregnancy.

2.2. 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. Physical activity during depression was assessed using a 6-point Likert scale with descriptors ranging from “never” (Bjorntorp and Rosmond, 1999) 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.

2.3. 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). Factors of the metabolic syndrome (MetS) were determined according to ATP-III criteria (FORD et al., 2002).

2.4. Magnetic resonance imaging

Intra-abdominal fat (Viscogliosi et al., 2014), subcutaneous fat (SCF), adrenal gland volume (AGV), and muscle mass were examined using a 1.5 T MRI scanner (Avanto, Siemens Healthcare, Germany). To quantify IAF and muscle mass the T1-weighted 3D Volume Interpolated Breathold Examination (VIBE) Dixon sequence was acquired between the diaphragm and the pelvic floor in an axial orientation using the following specifications: TR = 7.5 ms, TE = 2.4 and 4.8 ms, flip angle = 10°, matrix = 320 × 159, field of view = 400–460 mm, slice thickness = 5 mm. In-phase, out-of phase, fat and water images were calculated. Volume of IAF, SCF and muscle mass was determined from fat images by semi-automatic segmentation using MeVisLab 2.8 vc12-64 (MeVis Medical Solutions AG, Bremen, Germany). IAF and SCF segmentation was standardized by including all slices between the lower border of the heart and the L5/S1 joint. Muscle mass calculation was