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Adrenal Gland Volume and its Association with Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder

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INTRODUCTION

Epidemiology of Depression

Depression is a global, highly prevalent and clinically heterogeneous mental condition which is thought to result from interaction of multiple genes with environmental factors (1,2). It is estimated that depression affects 350 million people across the world (3). According to the International Consortium of Psychiatry Epidemiology surveys – established by the World Health Organization (WHO) and carried out between 1990 and 1999 on the worldwide-based sample size of 37,000 – the lifetime prevalence of major depressive episode varies widely depending on the world region; from 3% in Japan to 16.9% in the United States, with most countries confining to the range of 8-12% (4). Other important initiative recently investigating the prevalence in Europe – the European Outcome of Depression International Network (ODIN) study – found an average total prevalence of depressive disorders in Europe to be 8.6% (5). Depression is not only highly prevalent on a global scale but it also strongly influences the affected individual´s quality of life, significantly contributing to the global burden of disease. According to the report of the Global Burden of Disease Study 2010, depressive and other mental disorders are the leading global cause of all non-fatal burden of disease, expressed and measured in *years lived with disability* (YLDs) (6). Altogether, mental and substance use disorders account for 7.4% of all *disability adjusted life years* (DALYs) worldwide, representing the fifth leading disorder category of global DALYs (6). Within that group, depressive disorders account for most DALY´s (40.5%) (6). It is important to note that both prevalence and measures of burden (e.g. YLDs) have increased compared to existing data from 1990 (6). The tendency to increase will most probably persist and it has been predicted that by 2030, depression will be the second leading cause of illnesses worldwide, following HIV/AIDS and preceding ischaemic heart disease (7). In 2012, WHO announced that *´´the demand for curbing depression and other mental health conditions is on the rise globally´´* and that *´´on an individual, community and national level, it is time to educate ourselves about depression and support those who are suffering from this mental disorder´´* (3).

Introduction to Affective Disorders

Major depressive disorder (MDD) belongs to a group of *affective disorders* (also known as *mood disorders*) (8). As described by Kaplan and Sadock, *mood* is a state of mind – or feeling – experienced internally, which influences a person´s perception of the world. *Affect* is defined as the external expression of mood (9). All healthy individuals experience a wide variety of moods and dispose of a large repertoire of affective expressions. Healthy individuals are in control of their moods and affects, whereas patients suffering from mood disorders are characterized by loss of that control leading to a subjective experience of distress (9). Affective disorders involve a heterogeneous pool of symptoms occurring in various combinations and thus resulting in different affective conditions. Symptoms associated with affective disorders include those closely connected to emotions (e.g. feeling of guilt or sadness), cognitive impairments, and vegetative or other somatic manifestations (such as sleep or appetite disturbances) (1,9).

Diagnostic Criteria and Classification of Major Depressive Disorder

The diagnosis and classification of MDD and other affective disorders have long been posing difficulties while diagnostic approaches and classification systems have frequently been revised (1,8). Confusion and controversy is caused by the diversity of clinical presentation, matter subjectivity, and the fact that etiology and pathogenesis of affective disorders remain largely unclear. The two major classification systems of international importance used in psychiatry are the Diagnostic and Statistical Manual of Mental Disorders (currently DSM-5, launched in 2013 by the American Psychiatric Association, ASA) and the Classification of Mental and Behavioral Disorders included in the International Classification of Diseases (currently ICD-10, dated from 1994, WHO) (1,9). Both ASA and WHO indicate the importance of having reliable and valid diagnostic criteria for depressive disorders and acknowledge the necessity for standardized, reproducible diagnostic tools for not only internationally consistent patient treatment, but also for research purposes (8).

The previous version of the DSM classification and diagnostic criteria – DSM-IV (launched

in 1994 and revised in 2000) – will be presented here since subjects in this study were diagnosed based on this edition of the manual. According to DSM-IV, mood disorders are divided into *bipolar* and *depressive disorders* as well as *mood disorders due to a general medical condition*, and *substance-induced mood disorders* (10). Bipolar disorders include *bipolar I*, *bipolar II*, *cyclothymic disorder* and *bipolar disorder not otherwise specified.* Even though bipolar and depressive disorders are separate diagnostic categories, MDD serves not only as a fundamental clinical entity among depressive disorders but is also an indispensable element in diagnosing bipolar disorders (10). Depressive disorders are characterized by – and that distinguishes them from bipolar disorders – a lack of manic, mixed, or hypomanic episode (10).

Depressive disorders are divided into *major depressive disorder* (MDD), *dysthymic disorder,* and *depressive disorder not otherwise specified* (10). The common feature of all depressive disorders is the feeling of sadness, feeling of emptiness, and irritability. These symptoms are accompanied by somatic and cognitive changes that significantly affect the individual´s capacity to function. The respective diagnosis is based on whether it is a single or recurrent episode, its current severity, presence of psychotic features, and remission status (10,11).

Major depressive disorder is diagnosed when at least one or more *major depressive episodes* have been observed. The episode is characterized by depressed mood or loss of interest and/or pleasure in most activities. The diagnosis can be made when at least five out of nine symptoms are present over the course of at least two weeks (10). Table 1 displays a summary of DSM-IV diagnostic criteria for major depressive episode (10). Although a single episode with duration of two weeks' minimum is sufficient to make a diagnosis, in most cases the episodes last longer and the disorder has a recurring character. Nearly two-thirds of the subjects suffer from at least one recurrence within a period of ten years (12). With the increasing duration of recovery, the probability of recurrence decreases while each successive recurrence leads to an increase in recurrence probability (12).

Table 1: Diagnostic criteria for major depressive episode. Adapted from *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition: DSM-IV*

Five (or more) of the following symptoms present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood (1) or loss of interest or pleasure (2)
1. Depressed mood most of the day (e.g. sadness, emptiness, hopelessness) **2. Markedly diminished interest or pleasure in almost all activities** **3. Significant appetite changes or significant weight loss/gain** **4. Insomnia or hypersomnia** **5. Psychomotor agitation or retardation** **6. Fatigue or loss of energy** **7. Feelings of worthlessness or excessive guilt** **8. Diminished ability to think or concentrate, or indecisiveness** **9. Recurrent thoughts of death, suicidal ideation or a suicide attempt/plan**
The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
The episode is not attributable to the physiological effects of a substance, or to another medical condition

ICD-10 summarizes the major depression episode in a similar fashion, requiring the presence of four out of ten symptoms to make the diagnosis, including somatic symptoms (13).

Depression can manifest itself at all ages (9). The mean age of onset of MDD is 40 years and 50% of patients experience an onset between the ages of 20 and 50 (9). MDD is approximately twice as common in women as in men (9). Other identified socioeconomic correlates of MDD include low income, low educational level, and unmarried marital status (4). Interestingly, the generally accepted statement that urban communities have a higher risk for developing depression than rural ones, has not been sufficiently empirically supported (4,5,14). A recent epidemiological study with roughly 160,000 participants, performed across differently populated areas in the United States, showed

no depression risk differences between most rural and largest metropolitan areas (after statistical adjustment for other socioeconomic factors) (14). Also, prevalence figures in urban societies appear to vary markedly whereas figures collected among rural populations are more uniform, suggesting that risk factor profiles and cultural differences are less evenly distributed among urban societies (5). This demonstrates the complexity of depression´s epidemiology and exemplifies a challenge in approaching a study design involving depression.

Even though both DSM-IV and ICD-10 classification systems precisely define symptoms of depression and other psychiatric disorders, they hinder the so called *dimensional approach* to depressive phenotype since the existing subcategories are separate and mutually exclusive (2). As Korszun and colleagues argue, the dimensional approach, which allows symptom complexes to coexist to different degrees in individual patients, may be more useful in the understanding of the pathophysiology and the identification of susceptibility genes, i.e. genes that predispose to MDD (2). Neither ICD-10 nor DSM-IV classification system further addresses the distribution frequency of individual symptoms. Symptoms of individuals suffering from depressive disorders can vary markedly. Observing this variation is important for both understanding of the common clinical overlap between depression and anxiety (and other depression comorbidities) as well as the etiology of the disorders involved (2). For the time being, the DSM-5 and ICD-10 classifications are standard in both clinical as well as scientific fields of medicine.

Assessment Tools in Depression

Classification criteria for depression, such as these included in DSM-IV, can be complemented by a number of assessment tools which allow physicians to confirm the diagnoses and evaluate the severity of the disease in a practical, standardized and reproducible manner (8,9). These evaluation instruments can also be applied for assessment and documentation of progression — or regression — of the disease. Furthermore, due to high reliability and validity of these tests, they are suitable for characterization of patients recruited for clinical studies.

There are various types of such assessment tools, such as *self-report inventories*, *rating scales* or *semi-structured interview*s (8,9). To facilitate the diagnostic process based on the DSM, a *Structured Clinical Interview* has been developed. It is a semi-structured clinician-rated interview, which is not only used in clinical settings but has also been adapted for research purposes (8).

Assessment tools used for evaluating depression severity are either self-reported or clinician-rated (8,15). *Beck Depression Inventory* (BDI) is the most widely used self-reported tool for assessing the current severity of depression (8,9). It is a questionnaire relating to twenty-one symptoms such as sadness, suicidal thoughts, or loss of interest in sex. Each symptom includes four statements reflecting symptom severity. Patients are asked to choose the statements which best describe their feelings during the past two weeks (8,9). A frequently used clinician-rated assessment tool for depression severity is the rating scale developed by Montgomery and Åsberg (*Montgomery-Åsberg Depression Rating Scale,* MADRS) (15). Its structure is analogous to Beck Depression Inventory (10 items, instead of 21) and includes symptoms known to respond well to treatment, making it an especially suitable tool for disease monitoring in clinical trials (15).

Despite their similarities, clinician-rated and self-reported assessment tests each provide non-redundant and unique information. A complete and accurate assessment of depression should include both types of these tests (15).

Etiology and Pathogenesis of Depression

The etiology of MDD is complex and so far not well understood (1). Depression is considered to result from both genetic and environmental factors (1,16). The heterogeneous pathophysiology of MDD is reflected by numerous theories about its etiology (17).

Neurotransmitter Approach

Until recently, the monoamine neurotransmitter system abnormalities constituted the main focus of research on etiology of depression (9). The most studied and — in the

context of depression — best understood monoamine neurotransmitters are serotonin and norepinephrine (9). It has been shown that depletion of serotonin may trigger or advance depression, and that some patients with suicidal impulses have low concentrations of that neurotransmitter in the cerebrospinal fluid (9). The substantial therapeutic effect of the selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine) further supports the major role of serotonin in the pathophysiology of depression (9). The link between depression and norepinephrine has been suggested by basic studies showing decreased sensitivity of beta-adrenergic receptors and a good clinical response to antidepressants with noradrenergic effects (9). Other neurotransmitters which are most probably involved in the pathophysiology of depression are dopamine, histamine and acetylcholine. As an example, diseases linked to decreased concentration of dopamine, such as Parkinson´s disease, are known to be associated with depressive symptoms. On the contrary, drugs known to increase dopamine concentration, reduce the intensity of depressive symptoms (9). Furthermore, evidence exists that second messengers engaged in post synaptic signaling pathway cascade may be involved in pathophysiology of depression (9). Mood stabilizing drugs (also used in pharmacotherapy of depression) have been shown to directly act on G proteins and other second messengers, i.e. on proteins involved in the intracellular signaling cascade (9).

Currently, instead of focusing on a single neurotransmitter system in the research on depression etiology, a novel and more complex — a neurobehavioral and neuroregulatory — approach is favored (9,17).

Hormonal Disproportion

Both animal and human studies have shown that protracted stress can induce changes in the functional status of neurons and, eventually, cause cell death (9). The hyperactivity of the hypothalamus-pituitary-adrenal gland axis (HPA-Axis) is not only a hallmark of stress response (9) but is also apparent in depressed patients (18–21), thus serving as one of the clearest links between stress and depression (9). Mood changes are a prominent feature of Cushing´s syndrome, which usually presents with depressive symptoms (1). Multiple studies over the decades have demonstrated the HPA-axis

hyperactivity in depressed patients but mechanisms responsible for this abnormality still remain largely unclear (19,20). One of the leading hypotheses on this HPA-dysregulation is the impaired corticosteroid receptor signaling model (22). It implies that intracellular signaling of adrenocortical steroids is impaired in specific areas of the brain of depressed patients resulting in elevated production and secretion of corticotropin-releasing hormone (CRH). This leads to the hyperactivity of the HPA-axis with its subsequent somatic complications while the overproduction of CRH in the central nervous system causes the well documented neuropeptide imbalance (see *Neurotransmitter Approach*) in depressed patients (22). Currently, mouse genetics experiments are in progress aiming to identify the genes responsible for the impaired function of the corticosteroid receptor (22).

Other hormonal imbalances, such as elevated basal thyroid stimulating hormone (TSH) and reduced concentrations of triiodothyronine (T_3), have also been reported in patients with depression (1,9). Disturbance in hypothalamic-pituitary-thyroid system and other systems (such as those involving prolactin or growth hormone), have been subject to less intensive scrutiny in research on MDD pathophysiology. It is not known to what extent any of these changes play a pathogenic role in depressive syndromes (1,9).

Sleep Architecture Disturbances

A lot of attention has been paid to abnormalities in sleep architecture analyzed with help of electroencephalographic (EEG) techniques in depressed patients (1,9). It has been consistently observed that patients with MDD display reduced time between onset of sleep and first appearance of rapid eye movement (REM) phase (1,9,23). This *reduced REM latency*, and other EEG sleep abnormalities — such as deficits of *slow wave* sleep and elevated *REM density* — persist not only during depressive episodes but also throughout remission periods and remain an inexplicable trait of depressed patients (23). Interestingly, this trait is also present in healthy relatives of patients with depression and it has been found to be predictive of this disorder (23).

Susceptibility Genes

In the investigation of heritability of MDD and other mood disorders, numerous family,

adoption and twin studies have been conducted in order to address the question of whether, and to what extent, the disorder is familial (1,9,16). Family studies showed that a child of a parent with mood disorder has an increased risk for developing a mood disorder (1,9,16,24). The more members of the family are affected, the greater the risk is to a child (1,16,24). Family studies alone, however, do not separate the genetic from environmental factors, hence are insufficient to ultimately confirm and quantify the heritability in disease etiology. Adoption studies have confirmed that MDD is familial (1). The most powerful study design to evaluate environmental and genetic roles in the etiology of a disease are twin studies (1). Such studies showed an estimated heritability of major depression to be in the range of 31-42% (16). The meta-analysis of heritability studies performed by Sullivan and colleagues demonstrated that ´´*major depressive disorder is a complex disorder which does not result from either genetic or environmental influences alone, but rather from both*´´ (16). The studies on heritability of MDD, as well as the fact that existing data are mathematically incompatible with a single gene model, suggest that it is a polygenic disorder (i.e. it results from combined effects of many genes) (1).

The geneticists seeking genes involved in the MDD etiology have been performing various studies for decades (1). The *linkage studies* performed with affected individuals and their families, using genetic markers evenly spread throughout the genome, helped to establish candidates for susceptibility genes (1,25). *Association studies* comparing the variations within candidate genes in affected subjects versus controls, involve studying the genetic polymorphisms of susceptibility genes (1). A recent meta-analysis of such studies summarized that there is significant evidence for six MDD susceptibility genes so far (26). The identified genes are known to be involved in essential and relevant biological pathways, such as dopaminergic neurotransmission or serotonin reuptake in the central nervous system (25,26). This outcome, though, appears to be rather limited in contrast to the results of association studies on other psychiatric disorders such as schizophrenia or bipolar disorder (27). It is assumed that there are many more polymorphisms involved in the etiology of MDD (26).

With the emergence of the possibility to search the entire genome and the advent of

more powerful statistical methods, the search for susceptibility genes is about to be revolutionized (1,25). Among new approaches are the *gene-by-environment studies* which examine how genes can modify the effect of environmental factors on depression risk (and vice-versa) (25,27). So far, these studies suggest association with some genes involved in stress response regulation. However, these findings have not been fully consistent with association studies which concentrate on the same genetic loci (27). Because of the complex genetic architecture of depression, very large studies and approaches accounting for different forms of depression are needed (27).

Comorbidity of Major Depressive Disorder

Concept of Comorbidity

Comorbidity is most commonly defined as ``*a presence of additional diseases/conditions in relation to an index disease in one individual*`` (28). Studying comorbidity and related constructs such as *multimorbidity*, *patient complexity* and *frailty* can provide significant information about the etiology and pathophysiology of diseases as well as help improving disease management (28,29).

As summarized by Valderas and colleagues, disease coexistence may be a result of *chance*, *selection bias*, or *causal association* (28). The latter – representing a true etiological relationship - can be further divided into four models: *direct causality, associated risk factors, heterogeneity,* and *independence* (28). *Direct causality* implies that disease A directly leads to development of disease B. The *associated risk factors* model describes a relation in which a risk factor for disease A correlates with a risk factor known to be associated with the development of disease B, thus increasing the risk of simultaneous occurrence of diseases A and B. The *heterogeneity* model involves two — independent of each other — risk factors which both contribute to the development of disease A and B thus making the comorbidity of disease A and B more likely (28). Finally, in the *independence* (or ``distinct disease``) model, the simultaneous occurrence of two diseases is a result of an existence of a third distinct disease. For example, hypertension and chronic headache in a particular individual might be a result of pheochromocytoma (28).

The knowledge about comorbidity helps us to elucidate the pathophysiological mechanisms and to identify risk factors for the development of diseases. This, in turn, allows to improve treatment strategies and, even more importantly, initiate prevention (28–30) which has proven to be the most efficient way to approach health issues (31). We are currently in the process of translating our knowledge about co-occurrence of different diseases and the relationship between them into clinical management strategies (28). For example, such conditions as diabetes, hyperlipidemia or hypertension — belonging to a group of cardiovascular risk factors and sharing common pathophysiology — are frequently treated as a disease complex rather than individual entities.

Due to depression´s high global prevalence, its complex etiology as well as chronic character, interest in depression´s comorbidities is high and numerous studies investigating the comorbidities of depressive disorders have been conducted in the past decades.

Comorbidity of MDD can be divided into two groups: comorbidity with other psychiatric disorders, and with cardio-metabolic diseases.

Comorbidity of Major Depressive Disorder with Other Psychiatric Disorders

MDD is strongly comorbid with other psychiatric disorders (11,32,33). Frequently co-occurring psychiatric disorders are alcohol abuse or dependence, panic disorder, and obsessive-compulsive disorder (9,11,32). Conversely, individuals with substance use disorders and anxiety disorders show an elevated risk of current or lifetime comorbid anxiety disorder (9). Due to strong psychiatric comorbid associations of depression, it is considered advisable to perform screening tests for associated disorders in patients suffering from MDD (32). The lifetime risk of death by suicide among patients with major depression is reported to be 6% (34) and increased mortality associated with MDD is much accounted for by suicide (11). Also comorbid substance use disorders and anxiety disorders worsen the disease prognosis and markedly increase the risk of suicide (9).

Comorbidity of Major Depressive Disorder with Cardio-Metabolic Diseases

Depression has repeatedly been shown to be associated with coronary artery disease

(CAD), metabolic syndrome (MetS), type 2 diabetes mellitus, and stroke (33,35–39). The relationship is believed to have a bidirectional character (33,35–39).

Major Depressive Disorder and Coronary Artery Disease

There is a strong association between depression and CAD (33,36,37,40–44). A large amount of empirical data lead to the identification of depression as a risk factor for the development of CAD, as summarized in recent reviews (33,43–45). The overall relative risk (RR) for the development of CAD is increased in depressed and previously cardiologically healthy patients. According to the review by Rugulies, the adjusted RRs ranged from 1.5 to 4.16 (33). The cross-sectional studies summarized in a review by Lett and colleagues documented a disproportionately high point prevalence of depression among patients suffering from CAD, relative to the general population (14% to 47% among CAD patients as compared to 4% to 7% in a general population) (43). The prospective studies analyzed in the same review revealed a 1.5 to 2.0 increase of adjusted relative risk for CAD development in individuals suffering from depression (43). A combined overall relative risk for the onset of CAD in depressed patients, as estimated by Wulsin and Singal in their recent meta-analysis, was 1.6 (44). Additionally, it has been observed that this effect increases with severity and duration of depression, pointing to a possible dose-response relationship between MDD and CAD (33,46–48).

Major Depressive Disorder and Diabetes

Depression is also strongly comorbid with diabetes and, similarly to the co-occurrence of MDD and CAD, this relationship appears to be reciprocal (39,49–53). The apparent strong association between MDD and diabetes has been a subject of great interest of researchers for decades leading to the establishment of an international collaboration: the Dialogue of Diabetes and Depression (DDD) (51). This largest of its type initiative aims to raise awareness about these highly prevalent and strongly comorbid diseases and to improve their management in health services. The importance of that comorbidity lies also in the fact that the outcomes of each condition are worsened by the presence of the other (49,51,54).

Depression has consistently been demonstrated to predict the incidence of type 2 diabetes, as shown in a recent meta-analysis by Mezuk and colleagues (52). The studies

included in this review revealed a pooled relative risk of 1.6 to develop type 2 diabetes in individuals suffering from depression as compared with non-depressed individuals. However, only a modest association between diabetes and risk for depression has been observed in that meta-analysis (RR of 1.15) (52). The authors argue that diabetes predicting depression is an understudied phenomenon and that the relationship may be masked; depression in older adults is more difficult to detect and some risk factors for late-life depression, such as macrovascular disease compete with diabetes risk factors (52). A later meta-analysis on prevalence of depression among patients with diabetes estimated that diabetes doubles the odds of depression (50). Authors of another systematic review on that subject — Egede and Ellis — analyzed the association between depression and both types of diabetes and have also reached a conclusion that individuals with diabetes are more likely to have depression than individuals who do not have diabetes (53). Both reviews did not make a distinction between different diabetes types.

Major Depressive Disorder and Metabolic Syndrome

Another important aspect of the complex comorbidity of MDD with cardio-metabolic diseases is the co-occurrence of depression and metabolic syndrome (MetS). Numerous studies point our attention to the association between depression and metabolic syndrome (38,55–59).

A study conducted by Skilton and colleagues found that patients with depression are more likely to develop metabolic syndrome, and that this relationship is bidirectional (55). Also, Kahl and colleagues found the reciprocal relationship between lifetime major depression and MetS (38,60). These bidirectional influences persist being statistically significant after adjusting for a number of relevant risk factors such as age, gender, employment status, marital status, prior cardiovascular events, smoking status, BMI, and physical activity (55,60).

Major Depressive Disorder and Stroke

Recently two meta-analyses of prospective studies on depression being a predictor for stroke confirmed that depression is indeed associated with a significantly higher risk of stroke morbidity (61,62). In a review by Pan and colleagues, the pooled adjusted RR was

1.45 for any stroke event (total stroke: fatal, non-fatal, hemorrhagic, and ischemic) (61). When analyzing individual subgroups, pooled adjusted RR was (significantly) higher for fatal stroke and ischemic stroke, whereas results for non-fatal stroke and hemorrhagic stroke were not significant (61). An almost simultaneously performed meta-analysis by Dong and colleagues reported a relative risk for stroke development to be 1.34 as compared with healthy individuals (62). Additionally, the estimated risks were similar for both men and women (62).

Furthermore, evidence exists that a history of stroke increases depression incidence (63). As Dong and colleagues argue, the bidirectional character of this association still remains unclear since the possibility that undiagnosed stroke in study participants may have caused depression exists (62).

A recent study be Gilsanz and colleagues aimed to analyze whether stroke risk persists if depressive symptoms diminish or even completely remit (64). Addressing that question appears to be of high clinical relevance since it could reinforce the benefit of depression intervention as well as provide new insights into the mechanisms linking depression with stroke. Gilsanz and colleagues have shown that stroke risk remained elevated even if depressive symptoms were in remission for the consecutive 2 years of the study (follow-up period) (64). Additionally, they observed a dose-response relationship, analogous to the one hypothesized for the association of MDD with CAD. As the authors discuss, these results suggest cumulative etiological mechanism linking depression with stroke rather than short term processes or stroke triggers (64).

Major Depressive Disorder and Mortality

Major Depressive Disorder has been shown to be associated with increased risk of all-cause mortality (33,35,36,39,65–67). A systematic review by Schulz and colleagues examining evidence regarding non-suicide mortality in depressed patients demonstrated RR values confining to the range of 1.5 - 2.5 in most studies (67). The excess mortality observed in depressed patients is known to be caused not only by suicide but to primarily result from cardiovascular diseases (33,35,36,39,65–67). Even though increase in mortality caused by cardiovascular disease is to be expected — bearing in mind the strong association with cardiovascular disease discussed earlier — the risk for premature death remains elevated even after adjusting for cardiovascular and other metabolic

conditions as well as lifestyle factors (67).

Although the comorbidity of MDD and cardio-metabolic diseases has been thoroughly demonstrated, the mechanisms accounting for this co-occurrence remain mostly unclear (33,37,50,53,56,68). It is of extraordinary importance to investigate the causal link between MDD and cardio-metabolic diseases because of high prevalence of these diseases, their significant contribution to the global burden of disease, and the presence of efficient preventive methods for both depression as well as coronary artery disease and type 2 diabetes mellitus (3).

Understanding the Cardio-Metabolic Comorbidity of Major Depressive Disorder

A frequent co-occurrence of two or more diseases in the same individual raises the question whether there is an underlying common etiological pathway leading to the development of these conditions and whether the observed relationship has a causal character (28).

There are several theories about the pathophysiology of the association between MDD and cardio-metabolic diseases. It has been demonstrated that depressed subjects are more likely to have some of the well documented cardiovascular risk factors such as hypertension (69), habit of smoking (70), lack of leisure-time physical activity (35) as well as novel factors associated with cardiovascular disease such as elevated C-reactive protein (71). However, as mentioned previously, when adjusting for these risk factors (as well as other biological, behavioral and demographic factors) in the comparison of depressed versus non-depressed patients, the relative risk for development of CAD is still significantly elevated, suggesting existence of additional pathways in the pathophysiology of cardiovascular disease in patients suffering from MDD (33). Also, the link between depression and the development of diabetes type 2 remains significant after controlling for potential confounding factors such as age, race, gender, socioeconomic status, education, use of health services, and body weight (68).

There are numerous factors potentially contributing to the pathophysiology of

cardiovascular and metabolic diseases in depressed patients, many of them representing the novel neurobiological approaches towards MDD pathophysiology (33): hypercortisolism resulting from HPA-axis hyperactivity and other hormonal imbalances, dysregulation of inflammatory cytokines, glucose metabolism dysfunction as well as body composition changes such as increased pericardial and intra-abdominal fat.

Effects of Hypercortisolism

The HPA-axis hyperactivity is responsible for an increased release of catecholamines and corticosteroids which have been found to have an adverse effect on hemodynamics, contribute to intima injuries, and lead to other metabolic changes associated with cardiovascular risk (20,33). In particular, hypercortisolism has been discussed to contribute to insulin resistance, glucose intolerance, hypertension, and central obesity, i.e. to factors strongly associated with cardio-metabolic diseases (72).

Blood glucose levels are a result of a balance between insulin-dependent glucose production and secretion as well as glucose utilization (uptake of glucose by muscle tissue) (73). Corticosteroids affect glucose metabolism in a multifactorial manner: they increase hepatic gluconeogenesis, decrease insulin-dependent glucose uptake in peripheral tissues (mainly muscles) as well as inhibit insulin biosynthesis and secretion from the pancreatic β-cells (73). These effects are reached via multiple mechanisms such as influence on gene expression as well as direct inhibition or activation of various proteins involved in cellular pathways of different tissues. It is the balance of all the effects of glucocorticoids which determines whether the resulting insulin resistance is accompanied by hyperglycemia or rather hyperinsulinemia (73).

The effect of elevated corticosteroids on body fat is mainly mediated by the activation of lipoprotein lipase as well as the insulin dependent inhibition of lipid mobilization. Since the distribution of corticosteroid receptors in intra-abdominal and visceral adipose tissue is higher than in the subcutaneous adipose tissue, hypercortisolism leads to a more accentuated accumulation in these fat depots (74–76). Additionally, inhibition of growth hormone as well as pituitary gonadal inhibition — both resulting from HPA-axis hyperactivity — further enhance accumulation of visceral fat (74). This is due to the

growth hormone´s inhibiting effect on lipoprotein lipase activity as well as sex steroid hormone´s permissive effect on growth hormone´s activity in the visceral adipose tissue (74).

The association of hypertension with HPA-axis hyperactivity has been considered to be not only a consequence of hyperinsulinemia (secondary hypertension) but also result from the activation of the central nervous system (primary hypertension) since the sympathetic nervous system appears to be functionally coupled with the HPA-axis (74,77).

Dysregulation of Inflammatory Cytokines

Numerous cross-sectional studies suggest that depression is accompanied by immune dysregulation and activation of the inflammatory response system (78–80). A meta-analysis by Dowlati and colleagues reported a significantly higher concentrations of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) in depressed subjects compared with control subjects (78). Both these molecules act as acute-phase proteins and are secreted into the bloodstream in response to immunologic challenge. Elevation of TNF-α and IL-6 in the absence of infection is known to be involved in the pathogenesis of CAD. Thus, it is postulated that they may represent an important mediating factor between depression and cardio-metabolic morbidity (78). In the meta-analysis by Valkanova and colleagues, elevated CRP and IL-6 levels were demonstrated in depressed patients (80). Another meta-analysis, performed by Howren and colleagues additionally identified a strong association of depressive symptoms with elevated IL-1 (79). In order to evaluate the directionality of the relationship between depression and inflammation, a first prospective study on that matter has recently been conducted (81). Longitudinal associations between depressive symptoms and IL-6 as well as CRP were evaluated in a healthy population sample in this 6-year prospective cohort study (82). The results of this study imply that depression may lead to, rather than result from, augmented inflammation: depressive symptoms at baseline were a predictor of IL-6 while IL-6 did not predict the development of depressive symptoms. The results for the association of CRP with depression showed a weak bidirectional relationship, however, both associations were not-significant (82). Inflammation might

be one of the mechanisms accounting for excessive cardio-metabolic morbidity among depressed patients.

It has also been shown that depressed patients are more likely to have increased platelet activation and diminished heart rate variability, both phenomena being associated with atherosclerosis (33).

Body Composition Changes: Intra-abdominal and Pericardial Adipose Tissue

An increase in intra-abdominal and pericardial adipose tissue volumes — previously documented in depressed patients (83–88) — is a novel and presumably very important aspect of cardio-metabolic risk elevation in this patient group. These metabolically active fat depots are believed to play a role in linking depression with cardiovascular disease (84,86).

Human fat depots are divided into *brown* and *white adipose tissue* (89,90). Brown adipose tissue is present in very small quantities, mainly in infants and slim adults, and is mostly responsible for enhancing thermogenesis when the body is exposed to cold temperatures. It is also known to improve insulin sensitivity, glucose tolerance and is thus considered to be beneficial (90).

Vast majority of human adipose tissue consists of white type adipose tissue. It is mainly located beneath the skin (*subcutaneous adipose tissue*, ScAT; providing insulation) but also around internal organs (*visceral adipose tissue*; serving as a protective paddling). Visceral adipose tissue — also known as ectopic fat — includes *intra-abdominal adipose tissue* (IAT) and *pericardial adipose tissue* (PAT) (89,90). Some inaccuracies concerning the latter term are noticeable in existing literature; here it is referred to *pericardial adipose tissue* as the sum of *epicardial adipose tissue* (deposited directly on myocardium, beneath the visceral pericardium) and *paracardiac adipose tissue* (deposited outside of the parietal pericardium).

The main metabolic function of white type adipose tissue is to store free fatty acids during postprandial phase and to release them during fasting state as a source of energy to the organism (89). Like the brown adipocytes, the white fat cells also possess

additional metabolic functions and produce and secrete a number of different molecules called *adipokines* (also known as *adipocytokines*) (90). ScAT and visceral fat depots vary significantly in their endocrine effects since the variety and amount of adipokines they secrete differ substantially. ScAT is considered beneficial, primarily secreting *leptin* (involved in hunger inhibition) and *adiponectin* (indirectly enhancing insulin action and possessing anti-inflammatory effects). The ectopic fat depots, on the other hand, are known to have adverse metabolic effects and are associated with insulin resistance, dyslipidemia and increased cardio-metabolic risk (90). They primarily secrete adipokines which have negative effects on the metabolic, inflammatory, and vascular pathways in the entire organism. Some of these molecules, such as plasminogen activator inhibitor type-1 (PAI-1), TNF-α, IL-1 and IL-6, are known to be also produced elsewhere in the organism (89). Other adipokines, such as *resistin* — considered to be one of the major promoters of atherosclerosis (91) — are specific to these adipocytes (89).

The knowledge about different types of adipose tissues and their contrasting metabolic effects shed light on the clinical phenomenon — observed over two decades ago — that individuals having the same total amount of fat can demonstrate markedly different cardio-metabolic risk profiles, even after adjusting for other known risk factors (92). With the help of imaging techniques such as computed tomography or magnetic resonance imaging, the excess of individual adipose tissue compartments could be quantified and it was demonstrated that solely the visceral adipose tissue, and not the subcutaneous fat, is associated with increased cardio-metabolic risk (89,92). Hence, the term ``healthy`` obese phenotype characterized by a proportionally greater accumulation of ScAT was coined, as opposed to ``unhealthy`` obese phenotype with proportionally greater ectopic fat deposition (89,93). The visceral adipose tissue has become an apparent link between obesity and cardio-metabolic risk and thus a target of extensive research (89).

Investigating the Link between HPA-Axis and Body Composition

Hypercortisolism resulting from the dysregulation of HPA-axis is thought to play an important role in the accumulation of IAT and PAT (94). Adrenal gland volumes positively and strongly correlate with dexamethasone-suppressed salivary cortisol and total daily

salivary cortisol (95), suggesting that adrenal gland volume could serve as a proxy marker for hypercortisolism (96). In order to further investigate the role of HPA-axis hyperactivity in promoting the increase in IAT and PAT depots, it is of great importance to examine if there is a correlation between adrenal gland volume and volumes of IAT and PAT in patients suffering from MDD.

So far, several studies examining the parameters of HPA-axis activity and IAT as well as PAT — either separately or simultaneously — in depressed patients have been conducted.

Enlarged adrenal gland size in patients suffering from MDD has been confirmed in two case-control studies out of three as concluded in a review by Kessing and colleagues (96). Eskandari and colleagues found that women with MDD have more abdominal fat than healthy controls (97), while Everson and colleagues documented increased visceral fat in women with depressive symptoms (98). Also, Greggersen and colleagues found increased visceral fat content in young depressed women (85).

So far, studies investigating visceral fat and adrenal gland volumes simultaneously have come to different results. Ludescher and colleagues found increased volumes of IAT and a positive correlation with adrenal gland size in depressed women (83). In another study on women suffering from MDD, Weber-Hamann and colleagues found elevated IAT volumes in patients with hypercortisolism (99). Kahl and colleagues found increased IAT in women with MDD as well as women comorbid with MDD and borderline personality disorder, but no significant correlation between morning cortisol concentration and IAT has been observed (100). Scharnholz and colleagues found that depressed patients without hyperactivity of the HPA-axis (as demonstrated by negative low-dose dexamethasone suppression test) show no increase in visceral fat volumes (101). Studies mentioned above measured visceral fat content using magnetic resonance imaging (MRI) technique. A need for a case-control study investigating the association of visceral fat and adrenal gland volumes in patients suffering from depression still exists.

Goal of the Study

The objective of the study presented here was to further elucidate comorbidity of depression with cardio-metabolic diseases by investigating HPA-axis hyperactivity and ectopic fat depots in patients suffering from MDD. Adrenal gland volume was regarded as a proxy marker for HPA-axis activation and determined with the use of the established and reliable technique of magnetic resonance imaging. Furthermore, it was investigated whether adrenal gland volumes correlate with ectopic fat depots.

Adrenal gland volumes were measured in MDD inpatients and healthy control subjects and compared with previously obtained data (84) on IAT, PAT, ScAT volumes as well as fasting cortisol, TNF-α, and IL-6 in both patient groups.

The primary hypotheses of this dissertation were: 1. adrenal gland volume is increased in patients with MDD and 2. adrenal gland volume positively correlates with IAT and PAT.

The author of this dissertation performed a comprehensive and critical review of up-to-date scientific literature on the subject matter, was thoroughly trained to learn adrenal gland volume measurement technique with the use of MRI, performed the measurements, analyzed and critically interpreted the self-acquired and pre-existing data (84) as well as drew conclusions about its scientific importance. The results presented here stem from joined contribution of multiple study group members and have been published in the Journal of Psychoneuroendocrinology, volume 58, in August 2015 (102). The author of this dissertation actively participated in the writing process of the publication mentioned above.

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MATERIALS AND METHODS

Subjects

27 hospitalized patients suffering from major depressive disorder (MDD group) as well as 19 healthy subjects, serving as a control group, were recruited for this case-control study.

MDD group consisted of 12 women and 15 men, all treated at the Department of Clinical Psychiatry, Social Psychiatry, and Psychotherapy at Hannover Medical School, Hannover, Germany. Subjects were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (10). To confirm the diagnosis, Structured Clinical Interviews for DSM-IV (SCID I/II; German version) were performed (103). All MDD subjects received psychopharmacological treatment: 12 were treated with selective serotonin reuptake inhibitors, 5 with selective serotonin and noradrenaline reuptake inhibitors, 3 with agomelatine, 1 with a dopamine and noradrenaline reuptake inhibitor, 2 with quetiapine, 2 with mirtazapine, 1 with a noradrenaline reuptake inhibitor, and 1 with a tricyclic antidepressant. Patients underwent extensive anamnesis as well as physical examination to assess their cardiovascular and metabolic health status. No evidence for coronary artery disease, previous myocardial infarction, or history of endovascular procedures was found.

The control group consisted of 9 women and 10 men. Subjects were recruited via university bulletin boards. With the use of standardized psychiatric interviews, it was documented that participants have no current or lifetime history of psychiatric disorder. Also, the absence of acute or chronic infectious disease, a lifetime autoimmune disorder or psychopharmacological treatment in history was confirmed.

The exclusion criteria for all study participants included *schizophrenia*, *mental retardation*, *bipolar disorder*, *current substance use disorder*, *eating disorders*, *borderline personality disorder*, *type 2 diabetes mellitus*, *lifetime or current cardiovascular disease*, *immune or autoimmune disease, pregnancy*, and *age younger than 18 years*.

The study protocol was approved by the local ethics committee. Written informed consent was obtained from all participants prior to the beginning of the study.

Behavioural Assessments

Depression severity in both groups was evaluated with the use of Montgomery-Åsberg Depression Rating Scale (MADRS, clinician rated, German version), and the Beck Depression Inventory (BDI, self-reported, German version) (104). Physical activity of the subjects was estimated based on the self-reported 5-point Likert scale, consisting of numbers with their corresponding descriptor ranging from 1 (“never”) to 5 (“very often”) (105,106). Smoking habits were described in pack-years (number of cigarettes smoked per day multiplied by smoking duration in years and divided by 20) (107). Alcohol consumption was quantified as a number of estimated standard drinks (ca. 10 g of alcohol per drink) (108) consumed per week.

Magnetic Resonance Imaging

Using a 1.5 Tesla MRI scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany), the following body compartment volumes in all study participants were quantified: adrenal gland volume, pericardial adipose tissue (PAT), intra-abdominal adipose tissue (IAT), and subcutaneous adipose tissue (ScAT). In order to prevent the observer-expectancy-effect, observers were blinded for the status of the sample (CG versus MDD).

PAT was defined as the sum of epicardial adipose tissue (fat depot internal to the fibrous layer of the parietal pericardium) and the paracardial adipose tissue (fat depot between the chest wall and the external layer of the pericardium) (84). The T1-weighted dark-blood turbo spin-echo sequences were obtained in an ECG-gated fashion, in short- and long-axis views (TR/TE: 750/37 ms, flip angle: 180°, matrix: 384 x 187, field of view: 380 mm, and slice thickness: 10 mm). PAT volumes were calculated between the atrioventricular plane and the apex with the use of segmentation software QMass 7.1 (Medis, Leiden, the Netherlands).

For IAT and ScAT volume measurement, the T1-weighted 3D Volume Interpolated Breathold Examination (VIBE) Dixon sequences were obtained between the diaphragm and the pelvic floor (TR: 7.5 ms, TE: 2.4 and 4.8 ms, flip angle: 10°, matrix: 320 x 179, field of view = 400-460 mm, and slice thickness: 5 mm). IAT and ScAT volumes were determined with the use of semi-automatic segmentation software MeVisLab 4.6.2 (MeVis Medical Solutions AG, Bremen, Germany).

For the determination of adrenal gland volume, VIBE Dixon sequences were obtained (slice thickness: 2 mm). The volumes were calculated by manual segmentation with the use of QMass 7.1 software (Medis, Leiden, the Netherlands). The segmentation was performed twice by the same observer in order to gain intra-observer variability.

Blood Sampling

Via venipuncture, blood samples were withdrawn from all participants (collection time point: 7.00 – 8.00 A.M., stored at -80°C). In the so obtained fasting serum samples, concentrations of glucose, insulin and cortisol were determined (immunoassays from Roche Diagnostics, Mannheim, Germany). Furthermore, TNF-α- and IL-6- concentrations were measured with the use of high sensitivity ELISA kits (HS Quantikinine, R&D Systems, Wiesbaden, Germany).

Statistical Analysis

A statistical analysis of collected data points was performed with help of the SPSS software, version 22.0 (IBM corporation, Armonk, NY, the United States of America). Variables as well as covariates of the MDD and the control group were examined with the use of *analysis of covariance* (ANCOVA). In order to control for factors which may have influence on the formation of visceral fat depots, univariate analyses of covariance were performed. *Age, body weight* and *height* were defined as possible confounders.

For group characterization, definition of the metabolic syndrome according to ATP III criteria (109) was used. To compare the distribution of metabolic syndrome as well as gender distribution between the MDD and the control group, a chi-square test was performed.

In order to examine the correlation between adrenal gland volume and adipose tissue depots, partial correlation analysis with *age*, *body weight* and *height* as possible confounders was performed.

Obtained values were presented as *mean* ± *standard deviation* (SD). A significance level for all *P* values was determined to be <0.05.

RESULTS

Group Comparison

Distribution of various characteristics of subjects in each group, such as body weight or gender, was compared using a two-sided *t*-test. MDD group and the control group showed to be comparable in following categories: *gender distribution* (female percentage in CG: 47.4% versus 44.4% in MDD group), *age* (49 ± 14.3 vs. 43.4 ± 8.7 years), *body weight* (77.5 ± 18.4 vs. 78.8 ± 19.3 kg), *height* (1.76 ± 0.10 vs. 1.72 ± 0.08 m), and *body mass index* (24.8 ± 4.7 vs. 26.0 ± 4.2 kg/m^2). Furthermore, distribution of behavioural risk factors such as *alcoholic drinks per week* (3.5 ± 2.7 vs. 2.7 ± 4.8) or *percentage of smokers* (15.8% vs. 44.4%) was comparable between the groups (Table 2).

Assessment tools for depression severity (BDI-2 and MADRS) revealed that MDD group subjects indeed suffered from depression at the time of the evaluation whereas CG subjects did not (Table 2).

Adrenal Gland Volume

ANCOVA performed with *group* serving as independent variable, *total adrenal gland volume* as dependent variable, and *age*, *body weight* and *height* as covariates showed a significant effect of group (df = 1; F = 4.1; *P* <0.049) on total adrenal gland volume: MDD subjects had statistically significantly higher adrenal gland volumes than subjects of the control group. The same analysis performed for *left adrenal gland volume* instead of *total adrenal gland volume* as dependent variable showed an increase of body compartment in the MDD group which was not significant (df = 1; F = 3.5; *P* = 0.068). Analysis conducted with *right adrenal gland volumes* serving as a dependent variable demonstrated no effect of group (Figure 1).

Table 2: Anthropometric data, metabolic characteristics as well as fasting cortisol and TNF-α and IL-6 serum levels in patients with major depressive disorder compared with control group (mean ± standard deviation). *P* values <0.05 were considered significant. *Reprinted from Adrenal Gland Volume, Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder, by Kahl KG, Schweiger U, Pars K, Kunikowska A, Deuschle M, Gutberlet M, et al., 2015, Psychoneuroendocrinology, 58, p. 1–8. Copyright (2016), with permission from Elsevier*

	CG (n = 19)	**MDD (n = 27)**	***P* value**
Anthropometric data			
Female (N/%)	9 (47.4)	12 (44.4)	n.s.
Age (years)	49 ± 14.3	43.4 ± 8.7	n.s.
Weight (kg)	77.5 ± 18.4	78.8 ± 19.3	n.s.
Height (m)	1.76 ± 0.10	1.72 ± 0.08	n.s.
BMI (kg/m2)	24.8 ± 4.7	26.0 ± 4.2	n.s.
Physical activity (Likert scale*)	3.9 ± 1.3	2.8 ± 1.7	n.s.
Alcoholic drinks/week (N)	3.5 ± 2.7	2.7 ± 4.8	n.s.
Smoker (N/%)	3 (15.8)	12 (44.4)	n.s.
BDI-2 (sum)	0.8 ± 1.1	31.7 ± 9.2	**<0.001**
MADRS (sum)	0.7 ± 1.4	22.8 ± 7.1	**<0.001**
Metabolic characteristics			
Waist circumference (cm)	91.7 ± 15.0	93.7 ± 17.0	n.s.
HDL (mmol/L)	1.46 ± 0.39	1.35 ± 0.25	n.s.
Triglycerides (mmol/L)	1.25 ± 0.96	1.59 ± 0.72	n.s.
Systolic BP (mmHg)	128.9 ± 9.0	128.8 ± 18.4	n.s.
Diastolic BP (mmHg)	79.7 ± 6.7	81.4 ± 8.7	n.s.
Glucose (mmol/L)	5.22 ± 0.61	5.38 ± 0.68	n.s.
Insulin (mU/L)	8.9 ± 4.7	12.7 ± 6.9	**0.04**
Number of MetS criteria met	1.0 ± 1.1	1.4 ± 1.3	n.s.
MetS (N/%)	2 (10.5)	6 (22.2)	n.s.
Cortisol and cytokines			
Cortisol (nmol/L)	412.3 ± 123.4	556.7 ± 150.5	**0.001**
IL-6 (pg/mL)	1.8 ± 1.4	1.9 ± 2.2	n.s.
TNF-α (pg/mL)	0.8 ± 0.5	1.9 ± 1.8	**0.013**

CG control group, *MDD* major depressive disorder group, *n.s*. not significant, *BMI* body mass index, *BDI-2* (sum) Becks Depression Inventory-2 sum score, *MADRS* (sum) Montgomery-Åsberg Depression Rating Scale sum score, *HDL* high density lipoprotein, *BP* blood pressure, *MetS* metabolic syndrome, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha * Likert scale´s descriptors of physical activity range from 1 ``never`` to 6 ``very often

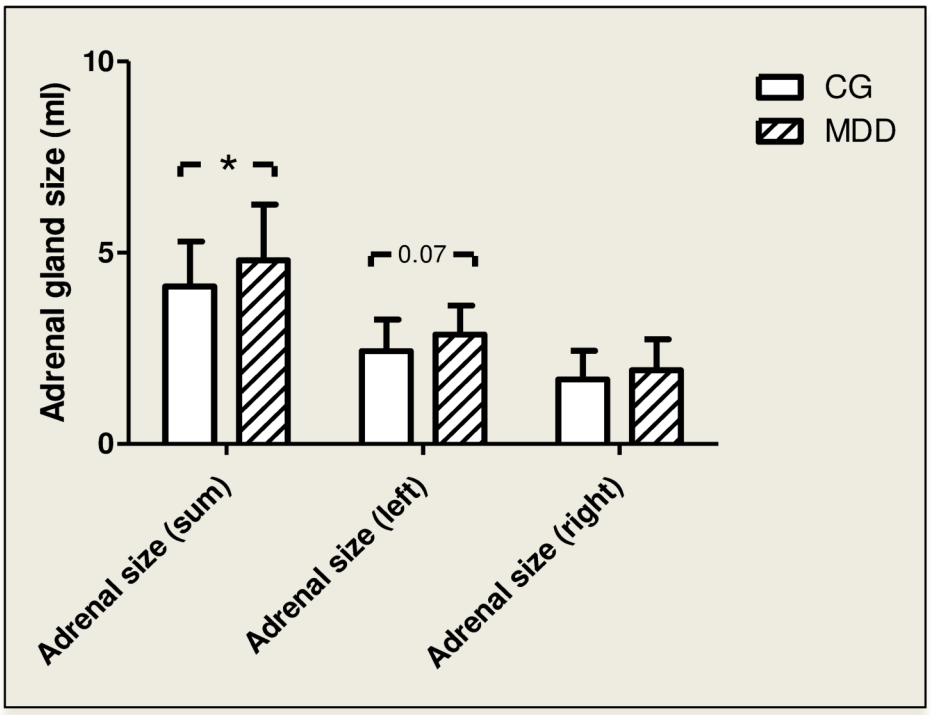

Figure 1: Morphometric analysis of adrenal gland size of patients suffering from major depressive disorder (MDD) compared with control group (CG). Volumes determined by magnetic resonance imaging. ANCOVA was performed for the sum of adrenal glands on both sides (sum) as well as separately for left and right adrenal gland volumes. *Reprinted from Adrenal Gland Volume, Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder, by Kahl KG, Schweiger U, Pars K, Kunikowska A, Deuschle M, Gutberlet M, et al., 2015, Psychoneuroendocrinology, 58, p. 1–8. Copyright (2016), with permission from Elsevier*

* indicates significance level of <0.05

Pericardial and Intra-abdominal Adipose Tissue

ANCOVA performed with *group* serving as independent variable, *pericardial adipose tissue* (PAT) as dependent variable, and *age*, *body weight* and *height* as covariates demonstrated significantly increased PAT volumes in MDD group (df = 1; F = 6.5; *P* = 0.014). In a similar analysis performed with *intra-abdominal adipose tissue* (IAT) as dependent variable in the ANCOVA model, a trend towards increased IAT in the MDD group was observed (df = 1; F = 3.1; *P* = 0.086). No effect of group was shown when ANCOVA for *subcutaneous adipose tissue* (ScAT) as dependent variable was performed (df = 1; F = 0.1; *P* = 0.72) (Figure 2).

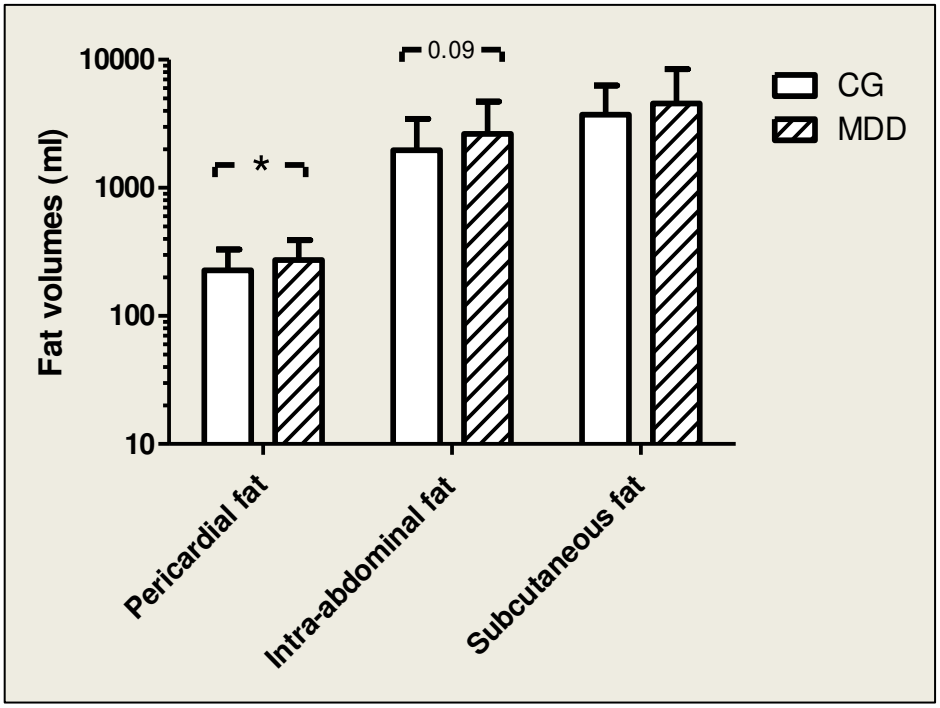

Figure 2: Morphometric analysis of pericardial, intra-abdominal and subcutaneous fat volumes of patients suffering from major depressive disorder (MDD) compared with control group (CG). Volumes determined by magnetic resonance imaging. *Reprinted from Adrenal Gland Volume, Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder, by Kahl KG, Schweiger U, Pars K, Kunikowska A, Deuschle M, Gutberlet M, et al., 2015, Psychoneuroendocrinology, 58, p. 1–8. Copyright (2016), with permission from Elsevier*

* indicates significance level of <0.05

Correlation between Adrenal Gland Volume and Ectopic Fat

Using partial correlation analysis with *age*, *body weight* and *height* as confounders it was shown that *total adrenal gland volum*e significantly and positively correlates with *intra-abdominal adipose tissue* (partial correlation coefficient: 0.3; df = 41; *P* = 0.049) as well as with *pericardial adipose tissue* (partial correlation coefficient: 0.5; df = 41; *P* = 0.001) when MDD group and control group are merged (Figure 3a/3b). The same partial correlation analysis performed in MDD group and control group separately showed no statistically significant correlation (data not shown).

No correlation between *total adrenal volume* and *subcutaneous adipose tissue* or *cortisol* was demonstrated (data not shown).

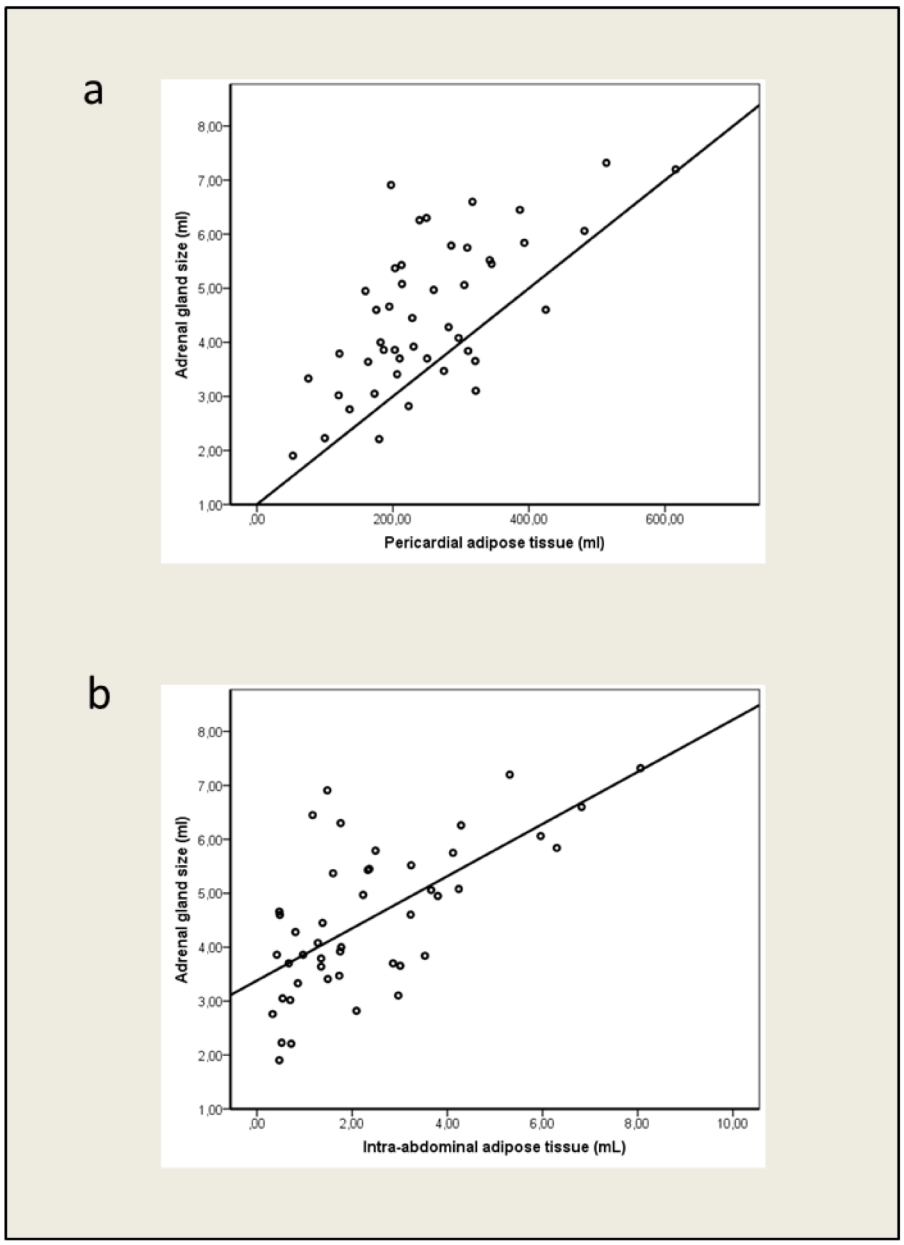

Figure 3a/3b: Correlation between adrenal gland size and pericardial adipose tissue (correlation coefficient: 0.3) (a) and between adrenal gland size and intra-abdominal adipose tissue (correlation coefficient: 0.5) (b). *Reprinted from Adrenal Gland Volume, Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder, by Kahl KG, Schweiger U, Pars K, Kunikowska A, Deuschle M, Gutberlet M, et al., 2015, Psychoneuroendocrinology, 58, p. 1–8. Copyright (2016), with permission from Elsevier*

Cortisol and TNF-α

A two-sided t-test showed increased levels of fasting cortisol (T = 3.4; df = 44; *P* = 0.001) and increased TNF-α concentrations in depressed patients (Table 1).

DISCUSSION

Summary of Results

This study demonstrates significantly higher volumes of adrenal gland, pericardial adipose tissue, and — to a lesser extent — intra-abdominal adipose tissue in patients with major depressive disorder, compared with healthy individuals. Moreover, adrenal gland volumes positively correlate with visceral fat depots; both PAT and IAT.

Additionally, statistically significant elevation of fasting cortisol and TNF-α in serum samples of patients with MDD has been demonstrated.

No increase in ScAT and no correlation between adrenal gland volume and ScAT have been found.

Increased Volumes of Adrenal Gland and Visceral Fat

The observation of increased adrenal gland volumes in patients with MDD is in accordance with results of other research groups (18,110,111). As reviewed by Kessing and colleagues, all three studies of adrenal gland volumes conducted to date in patients suffering from unipolar depressive disorders, documented enlarged adrenal glands, though in one study the increase was not statistically significant (96). The study by Nemeroff and colleagues included 38 patients as well as 11 controls and demonstrated a 50% increase of the adrenal volume in depressed patients, as measured by computed tomography (CT) (110). The study by Rubin and colleagues included 35 subjects in each group and demonstrated, with the use of MRI, a 38% increase of adrenal gland volumes in depressed patients (18). Also in the study by Amsterdam and colleagues adrenal gland volume, as measured by computed tomography, was elevated in depressed patients but not significantly (111). Because of large heterogeneity of study designs, it was not possible to perform a meta-analysis (96). Kessing and colleagues concluded that it still remains unclear whether HPA-axis hyperactivity — so consistently documented in patients suffering from depression — results in adrenal gland enlargement (96).

The study presented here provides further evidence that adrenal gland volumes are indeed increased in patients with major depressive disorder.

Also, the observed increase of IAT volumes in depressed patients, though statistically not significant, is in accordance with findings of other research groups (83,85,88,97–99,112). These metabolically active fat depots serve as an apparent risk factor for CAD and type 2 diabetes; it is believed that they play a role in linking depression with cardio-metabolic diseases (84,85,89,99).

Most importantly, this study demonstrates a statistically significant increase of PAT volumes in patients with MDD. Similarly to IAT, PAT enlargement is strongly associated with increased cardiovascular risk, even after adjusting for other cardiovascular risk factors (84,86,112–114). This alteration in body composition of depressed patients is a novel finding, substantially contributing to the understanding of cardio-metabolic comorbidity in patients suffering from depression (84).

No difference in ScAT volumes of patients with MDD compared with control group has been observed. This result was anticipated since groups were shown to be comparable concerning gender distribution, age, body weight, height and BMI, i.e. factors known to have influence on subcutaneous fat volumes.

Link between Visceral Fat and Cardio-Vascular Diseases

Several mechanisms linking visceral fat depots with development of atherosclerosis are being postulated. As discussed earlier, both IAT and PAT are known to have a strong endocrine, metabolic and inflammatory activity playing a systemic role in the development of cardio-vascular diseases (89,90). This is mediated by the secretion of various cytokines and other inflammatory molecules, such as TNF-α, IL-1 and IL-6, into the bloodstream (89,90).

Epicardial fat depots are believed to exert an additional paracrine proatherogenic effect on coronary vessels in the areas where no fascia separates the adipose tissue surrounding the heart from the adventitia of the arteries (89,115,116). These local effects include an attraction of inflammatory mediators to the adventitia resulting in the proliferation of vasa vasorum and the increase of subendothelial atherosclerotic

deposits, consequently leading to the development of atherosclerotic plaques (115). Epicardial adipose tissue of patients with CAD has been shown to express an increased amount of inflammatory humoral mediators whereas such changes are not being observed in the subcutaneous fat tissues of the same individuals (117). Also, a phenomenon of arterial remodelling — an important morphological change during development of atherosclerotic plaques — appears to be preferentially occurring in the lesions facing the pericardial side than those facing myocardial tissue (118,119) further supporting the proatherogenic role of ectopic fat tissue surrounding the heart.

Apart from high inflammatory activity, epicardial adipose tissue is known to exhibit an increased rate of lipolysis in comparison with subcutaneous adipose tissue, resulting in elevated concentration of saturated fatty acids (120). Saturated fatty acids can contribute to atherosclerotic development by exerting a direct toxic effect on vascular endothelial cells and thus prompting inflammation (120,121). Increased lipolysis in epicardial adipose tissue is believed to be caused by at least two mechanisms: lower anti-lipolytic effect of insulin on epicardial fat than on other fat compartments, and higher expression of β_3-receptors — known to be inducing lipolysis (122) — in that tissue (120,123).

According to the latest review by Iacobellis on local and systemic effects of epicardial adipose tissue, volume of this metabolically active fat compartment correlates with multiple factors involved in cardio-metabolic health: visceral adiposity, atherosclerosis, insulin resistance and fatty liver disease (116). Epicardial adipose tissue is increasingly regarded as an emergent tool for cardiovascular risk assessment.

Elevated Serum Cortisol

Statistically significant increase in fasting serum cortisol levels in the MDD group compared with control group has been demonstrated. Nevertheless, no correlation between plasma cortisol levels and adrenal gland volume has been observed. Likewise, other research groups investigating various measures of HPA-axis hyperactivity in depressed patients found no correlation between adrenal gland volume and cortisol concentration levels (18,96,110,111).

Lack of correlation between plasma cortisol and adrenal gland volume may result from the method used to determine cortisol activity. Although HPA-axis hyperactivity in patients suffering from depression is evident (18–21), some disagreement concerning the degree of that hyperactivity as well as suitable measurement methods, exist (20). Commonly, assessment of HPA-axis activity is performed by monitoring levels of its main effector molecule: cortisol (124). In blood, under physiological conditions, cortisol is primarily bound to cortisol-binding globulin (high affinity) and, to a much smaller extent, to albumin (weak affinity) (124). The remaining cortisol, the unconjugated molecule, like other components of blood plasma, undergoes filtration in glomeruli but the vast amount of that free cortisol is reabsorbed in the proximal tubule. Only a small fraction is eliminated from the organism with urine (124). The free cortisol in plasma undergoes strong physiological fluctuations throughout the day. Cortisol secretory bursts, following circadian rhythm, occur most frequently in the early morning hours and least frequently during later afternoon (125,126). Thus, due to physiological fluctuation, dependence on renal function and globulin binding capacity, as well as other potentially interfering factors, one-point cortisol measurement may not serve as a stable and reliable marker for HPA-axis activity.

The determination of cortisol concentration in blood serum as a daily profile is considered to reflect the factual hormonal status more accurately (125). Alternatively to this very strenuous method, a 0700-h and 2300-h salivary cortisol measurement can be used (127). Salivary cortisol can be collected outside of the hospital setting and without venipuncture and it has been shown to be stable for several days without processing (95). Salivary cortisol measurement is considered sensitive and reliable for detection of hypercortisolism and is a convenient and generally accepted procedure used for screening for Cushing syndrome (127,128).

Also, 24h urinary free cortisol determination (24h UFC) may — more precisely than one-point cortisol measurements — estimate the HPA-axis function (124). This method has an advantage of being unaffected by short-term fluctuations and plasma protein binding capacities discussed earlier (124). However, it is strenuous and does not provide any information about the diurnal fluctuations in cortisol secretion (124).

The one-point cortisol measurement performed in this study may not have been a method sufficiently accurate to evaluate HPA-axis hyperactivity.

Adrenal Gland Volume as a Marker for HPA-axis Hyperactivity

The HPA-axis hyperactivity in form of cortisol hypersecretion in depressed patients has been consistently demonstrated by elevated 24h UFC, serum- and cerebrospinal fluid cortisol concentrations (20,21,96,129). Adrenal gland volumes positively and strongly correlate with dexamethasone-suppressed salivary cortisol and total daily salivary cortisol (95), indicating that adrenal gland volume can serve as a reliable proxy marker for hypercortisolism (96). Consistent with these findings, adrenal gland volume has also been found to positively correlate with 24-h UFC concentration in patients with ACTH-dependent Cushing´s syndrome (130), further supporting the relationship between adrenal volumes and HPA-axis function. Interestingly, initially increased adrenal gland volume of a patient in the study mentioned above returned to normal as ACTH plasma levels decreased upon treatment (trans-sphenoidal surgery and subsequent pituitary irradiation) (130). This observation directly implies that ACTH plays an important role in adrenal growth.

The two main methods used to determine the adrenal gland volume are CT and MRI (131,132). A study by Rubin and colleagues compared the accuracy and reproducibility of adrenal gland volume assessment by CT and MRI already over 30 years ago (131). Using phantoms of known volumes of spherical and cuboid shapes embedded in a plastic tub of corn-oil margarine and thus simulating retroperitoneal fat, the precision of CT as well as MRI measurement could be assessed. On average, CT overestimated the calculated phantom volumes by 42% and MRI by 20% (131). Additionally, adrenal glands were measured in a group of healthy human subjects. Also in this *in vivo* assessment, the adrenal volume has been larger as measured by CT than MRI. All in all, MRI has been concluded to constitute a more precise technique for adrenal gland measurement than CT (131). Freel and colleagues have recently reassessed the continuously improving MRI-technique, analysing the accuracy and reproducibility of adrenal gland measurement with the use of MRI in the context of hypercortisolism (132). In the study design which

also involved adrenal phantoms they observed a disparity ranging from -7.4% and +9.3% between calculated and actual volumes (132). Additionally, intra- and inter-observer coefficients of repeatability were calculated. Authors concluded that most accurate and reproducible measurements of adrenal gland volumes are achieved when using a single observer with extensive experience. Furthermore, the obtained adrenal gland volumes significantly correlated with the sum of plasma cortisone and cortisol, supporting the evidence for a link between adrenal gland volume and hypercortisolism (132). Altogether, studies comparing precision of CT and MRI measurements of adrenal gland volumes showed that MRI yields more accurate results (131–133).

It is important to point out that other pathophysiological factors may exert influence on adrenal gland volume. It has been described that several endogenous factors, such as insulin-like growth factor 1 and angiotensin-2, as well as autonomic innervation of the adrenal cortex, may affect the adrenal gland size (18).

It is also unclear whether and to what extent psychopharmacological medication may affect the adrenal gland volume. Most studies assessing adrenal gland volumes in depressed patients examined individuals under heterogeneous pharmacological conditions and did not contribute any evidence of possible influence of drugs on adrenal gland volume (96).

Positive Correlation between Adrenal Gland Volume and Visceral Fat Volumes

Positive correlation of adrenal gland volumes with both PAT and IAT volumes constitutes an important result of this study, pointing to the pathophysiological link between hypercortisolism and increased cardiovascular risk. The association of HPA-axis hyperactivity with body composition changes known to be involved in the development of cardio-metabolic diseases provides an additional step in understanding the comorbidity of depression with CAD and type 2 diabetes mellitus. It suggests that chronic activation of stress response plays an important role in the development of cardio-metabolic diseases.

The statistically significant correlation between adrenal gland volume and ectopic fat depots, however, could not be demonstrated in the MDD group specifically. This may be caused by insufficient statistical power due to a small sample size (N = 27) and inability to perform subgroup analyses.

Recently, an association between HPA-axis activity and visceral fat has been observed in patients with adrenal incidentalomas. This patient group is known to have increased cardiovascular risk (134,135). It has been observed that individuals with adrenal incidentalomas and a mild serum cortisol elevation (post-dexamethasone cortisol values greater than 1.8 µg/dL) demonstrate increased intra-abdominal fat volumes (135). Also, pericardial fat volumes are significantly elevated in patients with incidentaloma and mild Cushing´s syndrome (134). These results not only reinforce the role of hypercortisolism and ectopic fat depots in the pathophysiology of cardiovascular diseases but also suggest that hypercortisolism precedes the accumulation of IAT and PAT.

Increased Levels of TNF-α

Significant increase in TNF-α level, as well as a slight but statistically insignificant increase in IL-6 level, in blood samples of depressed patients compared with control group, has been shown. As previously mentioned, elevated pro-inflammatory cytokines and other acute-phase proteins — such as CRP, TNF-α, IL-1 or IL-6 — is a consistent finding reported in patients with MDD (78,80,136). Recent meta-analysis of studies investigating cytokine levels in different subgroups of depressed patients revealed a dose-response relationship between depression and these inflammatory markers, suggesting that inflammation may be a result of depression (136). It has also been acknowledged that these cytokines play a vital role in the pathophysiology of cardio-metabolic diseases and thus it is believed that they may act as co-mediators between depression and cardio-metabolic diseases (78,136). As discussed earlier, ectopic fat is known to be secreting pro-inflammatory cytokines such as TNF-α (89). The results of this study point to the visceral fat as an important co-mediator between depression and cardio-metabolic diseases.

Study Limitations

The study presented here has several limitations.

Relatively small sample size in this case-control study is its most considerable restriction. It limits various subgroup analyses, such as those examining effect of age, body weight and severity or duration of depression. In particular, the stratification based on depression severity or duration would be of considerable interest with regard to observation that cardiovascular risk in depressed patients appears to display a dose-response character (33,46–48). Furthermore, recently, Kahl and colleagues demonstrated that chronic depression (defined as major depressive episode without remission for duration of at least two years) is associated with significantly higher PAT volume when compared with patients suffering from acute MDD (137). Patients with acute MDD also exhibited significantly higher PAT volume than non-depressed individuals but this effect was less pronounced in this group. These results not only emphasize the importance of PAT as a risk factor in cardiovascular disease but also draw attention to the role of depression chronicity in the mechanisms responsible for cardio-metabolic comorbidity of MDD. Due to limited group size in the study presented here, further stratification could not have been performed which may have left some correlations “unmasked”.

Furthermore, manual segmentation of small body compartments — such as ectopic fat depots or adrenal glands — is susceptible to motion artefacts, potentially leading to further sample size reduction during analysis.

In addition, 12 out of 27 patients within the MDD group were treated with psychopharmacological medication at the time of the examination. As discussed earlier, it remains an open question whether and to what extent psychopharmacological medication may influence adrenal gland volume or fat depots (96). It is known that several anti-depressants, such as amitriptyline, mirtazapine, and paroxetine, are associated with increased risk of weight gain (138,139). However, it is still unclear whether observed weight gain results in disproportionate accumulation of visceral fat. Thus, a study with medication-free subjects, such as patients newly diagnosed with

depression, would be desirable to circumvent the possible pharmacological effect of drugs on body composition.

Conclusion and Future Prospects

To conclude, results of this study support the observation that depressed patients display HPA-axis dysregulation and increased volumes of ectopic fat. The novel findings of this study are the increase of PAT volumes in patients suffering from MDD, as well as the positive correlation between adrenal glands and IAT and PAT volumes. The observed correlation suggests that HPA-axis hyperactivity with hypercortisolism may lead to the enlargement of ectopic fat depots, thus serving as a link between depression and increased cardio-metabolic morbidity.

Effect of Depression Intervention

The link between depression and cardio-metabolic diseases naturally leads to an assumption that treating depression may improve the cardio-metabolic outcome. Several studies analysed the effect of depression intervention on cardiac outcomes and mortality so far. The prospective multicentre clinical trial ENRICHD investigated whether patients with depression as well as patients with low social support after myocardial infarction profit from an intervention in form of cognitive behavioural therapy and, in some cases, sertraline medication (140). No difference in survival between the groups (those receiving therapy and those under standard care) has been demonstrated. The authors argued that the possible reason why the intervention failed to affect survival may lie in the enrollment of too many patients with mild or transient depression, as well as in the effect of treatment resistant depression (TRD) (140). The secondary analysis of data from the ENRICHD trial demonstrated that, after examining the difference between those who responded and those who did not respond to treatment, a significant reduction of mortality in successfully treated patients could be shown (141). These results are in accordance with the outcome of another clinical trial — SADHART — which assessed the cardiac outcomes in patients under sertraline therapy (142). Here patients suffering from major depressive disorder who responded to sertraline therapy exhibited a reduction of cardiovascular mortality as compared with therapy non-responders (142).

A third major prospective trial investigating the effect of depression therapy (Mirtazapine) on cardiac mortality and morbidity in post-myocardial infarction patients — MIND-IT — demonstrated no effect on the primary outcome in the form of recurrent cardiac events (143). As summarized in a recent Journal of Psychosomatic Research editorial by Shapiro, the trials conducted so far demonstrated a surprisingly weak and in general debatable effect of depression intervention on cardiac events or mortality (144). The author´s possible explanation to that, apart from several study design weaknesses, might be the insufficient depression intervention with minimal effect on the final study outcomes after short follow-up periods. Furthermore, Shapiro speculates that patients suffering from heart disease might differ from depressed patients without cardiovascular disease burden (144). It is important to point out that studies discussed so far concerned exclusively post-myocardial-infarction patients. A protective effect of depression intervention on the development of cardio-metabolic diseases may not yet have been unmasked. Big prospective studies with long follow-up periods are required.

Impact on Health Care Management

Understanding the link between depression and its comorbidity with cardio-metabolic disease may have an important impact on health care management. Medicine worldwide is undergoing a process of fragmentation into more specialized disciplines (51). This is mainly caused by two factors: increasing complexity of medical specialities and treatments, as well as increasing health literacy of populations and general access to the internet, frequently leading to self-diagnosis (51). More and more patients bypass the general practitioner and their illnesses are often treated solely in specialized centres. Specialized health services, in turn, are reluctant to treat comorbid diseases which are being outside of their scope of expertise. In order to improve the management of comorbid diseases, a complex and interdisciplinary approach is needed (28,51,145). New initiatives addressing the challenges of treatment of comorbid diseases are emerging worldwide. The Dialogue on Diabetes and Depression, as discussed earlier, is an international initiative aiming to raise awareness about the comorbidity of depression and diabetes and to improve their management in health services (51). It is expected that an increasing number of countries will join this and similar initiatives to

address one of the most important health care challenges of the 21st century: the growing complexity of medicine and health care. It would be advisable to include cardio-metabolic assessment into general treatment and diagnostic guidelines for patients suffering from depression. For example, easily accessible, fast and reasonably priced method of 2D echocardiographic quantification of epicardial fat thickness has been shown to be suitable for cardiovascular risk assessment (146). Epicardial fat thickness, determined by echocardiography, is known to independently reflect levels of intra-abdominal fat and myocardial fat content as measured by MRI (146).

Recently, it has been demonstrated that epicardial fat thickness, as measured by echocardiography, significantly decreases after bariatric surgery (147) or 6 months of low-caloric diet (148) in obese patients, pointing to possible application of this imaging technique for monitoring weight loss and cardiovascular risk stratification simultaneously.

In the future, it would be desirable to perform studies investigating whether body composition changes described here are reversible in patients suffering from depression. Monitoring these changes with the use of echocardiography or magnetic resonance imaging may be recommended to assess cardiovascular risk development in this patient group.

DISSERTATION SUMMARY

Adrenal Gland Volume and its Association with Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder

Introduction

Depression is a ubiquitous, highly prevalent and clinically heterogeneous mental condition affecting more individuals every year. It does not only influence mood but it also leads to cognitive and somatic changes significantly contributing to global disease burden. The basic clinical entity among depressive disorders is *major depressive disorder* (MDD).

MDD is strongly comorbid with cardio-metabolic diseases, such as coronary artery disease or type 2 diabetes mellitus, and has been identified to be a risk factor for development of these conditions. However, pathophysiological mechanisms responsible for increased prevalence of cardio-metabolic diseases in depressed patients remain mostly unclear.

Hyperactivity of hypothalamus-pituitary-adrenal gland axis (HPA-axis) with subsequent hypercortisolism has repeatedly been documented in patients suffering from depression. Increased cortisol levels are known to contribute to cardio-metabolic risk factors such as insulin resistance, glucose intolerance, and hypertension. Also, increased intra-abdominal adipose tissue (IAT) and, recently, pericardial adipose tissue (PAT) volumes have been observed in depressed individuals. Unlike subcutaneous adipose tissue (ScAT), these visceral fat depots are known to have adverse metabolic effects and are associated with insulin resistance and dyslipidemia.

Hypercortisolism is thought to play an important role in the accumulation of IAT and PAT in depression. However, studies investigating the association of HPA-axis activity with visceral fat depots in depressed patients have come to inconclusive results. This may have been caused by inadequate study designs as well methodological difficulty in quantifying hypercortisolism in an accurate and reproducible manner. Hypercortisolism and adrenal gland volume exhibit a strong positive correlation while MRI precision has noticeably improved in the past years allowing accurate and reproducible tissue

quantification. Hence, adrenal gland volume can be considered a reliable proxy marker for HPA-axis hyperactivity.

The study presented here aimed to further investigate the link between depression and cardio-metabolic diseases. With the use of MRI scanner, adrenal gland volumes were measured in patients with MDD and in a healthy control group. Subsequently, correlation between adrenal volume and previously obtained volumes of IAT, PAT and ScAT in same subjects was examined. Additionally, biochemical markers of inflammation and cortisol levels were measured in serum samples obtained from both groups.

Methods

27 patients with major depressive disorder (MDD group) as well as 19 healthy subjects (control group) were included in this case-control study. Participants underwent an extensive anamnesis as well as physical examination to assess their cardiovascular and metabolic health status. In both groups anthropometric data was collected and depression severity, physical activity, smoking habits as well as alcohol consumption was assessed. The main exclusion criteria for all study participants were confirmed cardio-metabolic disease, chronic infections and lifetime autoimmune disorders.

Adrenal gland volumes, PAT, IAT as well as ScAT in both groups were quantified with the use of MRI scanner. Further parameters examined included factors of the metabolic syndrome, fasting cortisol, fasting insulin, and pro-inflammatory cytokines.

Anthropometric data of the study groups was compared using a *two-sided t-test*. The effect of group on adrenal gland and quantified fat depots was analysed with the use of *analysis of covariance* (ANCOVA) while correlation between adrenal gland and individual fat depots was investigated using *partial correlation analysis*. Age, body weight and height were regarded as possible confounders.

Results

MDD group and control group were shown to be comparable regarding gender distribution, age, body weight, height and BMI. Significantly higher volumes of adrenal gland, pericardial adipose tissue, and — to a lesser extent — intra-abdominal adipose

tissue in patients with major depressive disorder have been observed, compared with healthy individuals. Adrenal gland volume positively correlates with both PAT and IAT in a joined group consisting of all study participants. Additionally, statistically significant elevation of fasting cortisol and TNF-α in serum samples of patients with MDD has been demonstrated.

No increase in ScAT volume and no correlation between adrenal gland volume and ScAT volume have been found in depressed patients.

Discussion

Results of this study support the observation that depressed patients display HPA-axis hyperactivity and increased volumes of ectopic fat. Moreover, the observed positive correlation between adrenal glands and IAT as well as PAT volumes suggests that HPA-axis hyperactivity may lead to enlargement of ectopic fat depots, possibly serving as a link between hypercortisolism and cardio-metabolic diseases. Lack of significant effect of group (MDD versus healthy individuals) on ScAT volume further supports the unique role of ectopic fat in mechanisms underlying cardio-metabolic comorbidity of depression. Volumetric measurements presented here are in agreement with increased levels of cortisol and TNF-α in the MDD group compared with healthy individuals.

The link between depression and cardio-metabolic disease may have an important impact on health care management. It reveals the importance of a complex and interdisciplinary approach to depression management. It is advisable to introduce cardio-metabolic assessment into general treatment and diagnostic guidelines for patients suffering from depression. With constantly improving MRI-technique, new diagnostic possibilities for early identification of depressed patients with increased cardio-metabolic risks may emerge.

In the future, early depression intervention may serve as means of primary prevention of cardio-metabolic diseases in that patient group. Studies investigating whether and to what extent body composition changes studied here are reversible, are still needed.

BIBLIOGRAPHY

1. Murray R, Murray RM, Kendler KS, McGuffin P. Essential Psychiatry. Cambridge University Press; 2008.

2. Korszun A, Moskvina V, Brewster S, Craddock N, Ferrero F, Gill M, et al. Familiality of Symptom Dimensions in Depression. Arch Gen Psychiatry. 2004;61(5):468–74.

3. Marcus M, Yasamy MT, van Ommeren M, Chisholm D. Depression, a global public health concern. WHO Dep Ment Heal Subst Abus. 2012;1–8.

4. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl R V., De Graaf R, Vollebergh W, et al. The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res. 2003;12(1):3–21.

5. Ayuso-Mateos JL, Vázques-Barquero JL, Dowrick C, Lehtinen V, Dalgard OS, Casey P, et al. Depressive disorders in Europe: Prevalence figures from the ODIN study. Br J Psychiatry. 2001;179(OCT.):308–16.

6. Whiteford H a., Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. Lancet. 2013;382:1575–86.

7. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):2011–30.

8. Hales RE, Yudofsky SC, Gabbard GO, Publishing AP. The American Psychiatric Publishing Textbook of Psychiatry. American Psychiatric Pub.; 2008. (American Psychiatric Publishing Textbook of Psychiatry).

9. Sadock BJ, Kaplan HI, Sadock VA. Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry. Wolter Kluwer/Lippincott Williams & Wilkins; 2007. (Kaplan & Sadock textbooks).

10. Association AP. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-

TR. American Psychiatric Association; 2000.

11. Association AP. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM 5.

12. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry. 2000;157(2):229–33.

13. Organization WH. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Royal College of Psychiatrists; 1992. (ICD-10 classification of mental and behavioural disorders / World Health Organization).

14. Breslau J, Marshall GN, Pincus HA, Brown RA. Are mental disorders more common in urban than rural areas of the United States? J Psychiatr Res. 2014 Sep;56:50–5.

15. Uher R, Perlis RH, Placentino A, Dernovšek MZ, Henigsberg N, Mors O, et al. Self-report and clinician-rated measures of depression severity: can one replace the other? Depress Anxiety. 2012 Dec;29(12):1043–9.

16. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. Am J Psychiatry. 2000;157(October):1552–62.

17. Pehrson A, Sanchez C. Altered γ-aminobutyric acid neurotransmission in major depressive disorder: a critical review of the supporting evidence and the influence of serotonergic antidepressants. Drug Des Devel Ther. 2015 Jan;9:603.

18. Rubin RT, Phillips JJ, McCracken JT, Sadow TF. Adrenal gland volume in major depression: relationship to basal and stimulated pituitary-adrenal cortical axis function. Biol Psychiatry. 1996 Jul 15;40(2):89–97.

19. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008 Sep;31(9):464–8.

20. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med.

2011;73:114–26.

21. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: Does cortisol play a role? Biol Psychiatry. 2004;55(03):1–9.

22. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology. 2000 Nov;23(5):477–501.

23. Modell S, Ising M, Holsboer F, Lauer CJ. The Munich vulnerability study on affective disorders: premorbid polysomnographic profile of affected high-risk probands. Biol Psychiatry. 2005 Nov 1;58(9):694–9.

24. McGuffin P, Katz R, Aldrich J, Bebbington P. The Camberwell Collaborative Depression Study. II. Investigation of family members. Br J Psychiatry. 1988 Jun;152:766–74.

25. Levinson DF. The Genetics of Depression: A Review. Biol Psychiatry. 2006;60(Mdd):84–92.

26. López-León S, Janssens a CJW, González-Zuloeta Ladd a M, Del-Favero J, Claes SJ, Oostra B a, et al. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry. 2008;13:772–85.

27. Dunn EC, Brown RC, Dai Y, Rosand J, Nugent NR, Amstadter AB, et al. Genetic Determinants of Depression [Internet]. Vol. 23, Harvard Review of Psychiatry. 2015 [cited 2015 Feb 22]. p. 1–18. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00023727-201501000-00001

28. Valderas JM, Sibbald B, Salisbury C. Defining Comorbidity: Implications for Understanding Health and Health Services. Ann Fam Med. 2009;(7):357–63.

29. De Groot V, Beckerman H, Lankhorst G, Bouter L. How to Measure Comorbidity a Critical Review of Available Methods. J Clin Epidemiol. 2003 Mar;56(3):221–9.

30. Stausberg J, Hagn S. New Morbidity and Comorbidity Scores based on the Structure of the ICD-10. PLoS One. 2015 Jan;10(12):e0143365.

31. Woolf SH, Atkins D. The evolving role of prevention in health care. Am J Prev

Med. 2001 Apr;20(3):13–20.

32. Usherwood T. Mood disorders in general practice. Med Today. 2014;15(5):2–6.

33. Rugulies R. Depression as a predictor for coronary heart disease. Am J Prev Med. 2002 Jul;23(1):51–61.

34. Inskip HM, Harris EC, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry. 1998 Jan;172:35–7.

35. Onge JM Saint, Krueger PM, Rogers RG. The Relationship Between Major Depression and Nonsuicide Mortality for U . S . Adults : The Importance of Health Behaviors. Journals Gerontol. 2014;69:622–32.

36. Surtees PG, Wainwright NWJ, Luben RN, Wareham NJ, Bingham S a, Khaw K-T. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. Am J Psychiatry. 2008;165(April):515–23.

37. Plante GE. Depression and cardiovascular disease: A reciprocal relationship. Metabolism. 2005;54(Suppl 1):45–8.

38. Kahl KG, Greggersen W, Schweiger U, Cordes J, Balijepalli C, Losch C, et al. Prevalence of the metabolic syndrome in unipolar major depression. EurArchPsychiatry ClinNeurosci. 2012;262(4):313–20.

39. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RIG, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC. Eur Psychiatry. 2009;24:412–24.

40. Rahman I, Humphreys K, Bennet AM, Ingelsson E, Pedersen NL, Magnusson PKE. Clinical depression, antidepressant use and risk of future cardiovascular disease. Eur J Epidemiol. 2013;28:589–95.

41. Elderon L, Whooley MA. Depression and cardiovascular disease. Prog Cardiovasc Dis. 2013 Jan;55(6):511–23.

42. Ziegelstein RC. Improving depression and reducing cardiac events: which is the chicken and which is the egg? J Psychosom Res. 2013 May;74(5):454–7.

43. Lett HS. Depression as a Risk Factor for Coronary Artery Disease: Evidence, Mechanisms, and Treatment. Psychosom Med. 2004;66(3):305–15.

44. Wulsin LR SB. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med. 2003;65(April):201–10.

45. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J. 2006 Nov 13;27(23):2763–74.

46. Brown JM, Stewart JC, Stump TE, Callahan CM. Risk of Coronary Heart Disease Events Over 15 Years Among Older Adults With Depressive Symptoms. Am J Geriatr Psychiatry. 2011 Aug;19(8):721–9.

47. Windle M, Windle RC. Recurrent depression, cardiovascular disease, and diabetes among middle-aged and older adult women. J Affect Disord. 2013 Sep;150(3):895–902.

48. Seldenrijk A, Vogelzangs N, Batelaan NM, Wieman I, van Schaik DJF, Penninx BJWH. Depression, anxiety and 6-year risk of cardiovascular disease. J Psychosom Res. 2015 Feb;78(2):123–9.

49. Holt RIG, de Groot M, Lucki I, Hunter CM, Sartorius N, Golden SH. NIDDK international conference report on diabetes and depression: current understanding and future directions. Diabetes Care. 2014 Aug;37(8):2067–77.

50. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The Prevalence of Comorbid Depression. Diabetes Care. 2001;24(6):1069–78.

51. Sartorius N, Cimino L. The Dialogue on Diabetes and Depression (DDD): Origins and achievements. J Affect Disord. 2012 Oct;142 Suppl:S4-7.

52. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes

over the lifespan: A meta-analysis. Diabetes Care. 2008;31(12):2383–90.

53. Egede LE, Ellis C. Diabetes and depression: Global perspectives. Diabetes Res Clin Pract. 2010;87(3):302–12.

54. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry. 2003 Aug;54(3):317–29.

55. Skilton MR, Moulin P, Terra J-L, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. Biol Psychiatry. 2007 Dec 1;62(11):1251–7.

56. Mcintyre RS, Rasgon NL, Kemp DE, Nguyen HT, Law CWY, Hbsc H, et al. Metabolic Syndrome and Major Depressive Disorder- Co-occurrence and Pathophysiologic Overlap. Curr Diab Rep. 2009;(9):51–9.

57. Liaw F-Y, Kao T-W, Hsueh J-T, Chan Y-H, Chang Y-W, Chen W-L. Exploring the Link between the Components of Metabolic Syndrome and the Risk of Depression. Biomed Res Int. 2015 Jan;2015:586251.

58. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in men. Am J Psychiatry. 2006;163(1):115–24.

59. Marazziti D, Rutigliano G, Baroni S, Landi P, Dell'Osso L. Metabolic syndrome and major depression. CNS Spectr. 2014 Aug;19(4):293–304.

60. Kahl KG, Schweiger U, Correll C, Müller C, Busch M-L, Bauer M, et al. Depression, anxiety disorders, and metabolic syndrome in a population at risk for type 2 diabetes mellitus. Brain Behav. 2015 Jan 21;n/a-n/a.

61. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011 Sep 21;306(11):1241–9.

62. Dong J-Y, Zhang Y-H, Tong J, Qin L-Q. Depression and Risk of Stroke: A Meta-Analysis of Prospective Studies. Stroke. 2011;43(1):32–7.

63. Huang C-Q, Dong B-R, Lu Z-C, Yue J-R, Liu Q-X. Chronic diseases and risk for

depression in old age: a meta-analysis of published literature. Ageing Res Rev. 2010 Apr;9(2):131–41.

64. Gilsanz P, Walter S, Tchetgen Tchetgen EJ, Patton KK, Moon JR, Capistrant BD, et al. Changes in Depressive Symptoms and Incidence of First Stroke Among Middle-Aged and Older US Adults. J Am Heart Assoc. 2015;4(5):e001923–e001923.

65. Brown ADH, Barton DA, Lambert GW. Cardiovascular abnormalities in patients with major depressive disorder: autonomic mechanisms and implications for treatment. CNS Drugs. 2009 Jan;23(7):583–602.

66. Houle JN. Depressive symptoms and all-cause mortality in a nationally representative longitudinal study with time-varying covariates. Psychosom Med. 2013;75(5):297–304.

67. Schulz R, Drayer RA, Rollman BL. Depression as a risk factor for non-suicide mortality in the elderly. Biol Psychiatry. 2002 Aug;52(3):205–25.

68. Rustad JK, Musselman DL, Nemeroff CB. The relationship of depression and diabetes: Pathophysiological and treatment implications. Psychoneuroendocrinology. 2011;36(9):1276–86.

69. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. Arch Intern Med. 2000;160:1495–500.

70. Covey LS, Glassman AH, Stetner F. Cigarette smoking and major depression. J Addict Dis. 1998 Jan 12;17(1):35–46.

71. Danner M, Kasl S V, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. Psychosom Med. Jan;65(3):347–56.

72. Wajchenberg BL. Subcutaneous and Visceral Adipose Tissue: Their Relation to the Metabolic Syndrome. Endocr Rev. 2000 Dec;21(6):697–738.

73. Giordano R, Guaraldi F, Berardelli R, Karamouzis I, D'Angelo V, Marinazzo E, et al. Glucose metabolism in patients with subclinical Cushing's syndrome.

Endocrine. 2012 Jun;41(3):415–23.

74. Björntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev. 2001;2:73–86.

75. Rebuffe-Scrive M, Walsh U a., McEwen B, Rodin J. Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. Physiol Behav. 1992;52(3):583–90.

76. Yoshida S, Inadera H, Ishikawa Y, Shinomiya M, Shirai K, Saito Y. Endocrine disorders and body fat distribution. Int J Obes. 1991 Sep;15 Suppl 2:37–40.

77. Reaven GM, Lithell H, Landsberg L. Hypertension and Associated Metabolic Abnormalities — the Role of Insulin Resistance and the Sympathoadrenal System. N Engl J Med. 1996;334(No.6):374–81.

78. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010 Mar 1;67(5):446–57.

79. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171–86.

80. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013 Sep 25;150(3):736–44.

81. Stewart JC, Zielke DJ, Hawkins M a W, Williams DR, Carnethon MR, Knox SS, et al. Depressive symptom clusters and 5-year incidence of coronary artery calcification: The coronary artery risk development in young adults study. Circulation. 2012;126:410–7.

82. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav Immun. 2009 Oct;23(7):936–44.

83. Ludescher B, Najib A, Baar S, Machann J, Schick F, Buchkremer G, et al. Increase of visceral fat and adrenal gland volume in women with depression: preliminary

results of a morphometric MRI study. Int J Psychiatry Med. 2008;38(3):229–40.

84. Kahl KG, Hueper K, Schweiger U, Gutberlet M, Detlef a. M, Weiss C, et al. Pericardial, intra-abdominal, and subcutaneous adipose tissue in patients with major depressive disorder. Acta Psychiatr Scand. 2014;130(1):137–43.

85. Greggersen W, Rudolf S, Fassbinder E, Dibbelt L, Stoeckelhuber BM, Hohagen F, et al. Major depression, borderline personality disorder, and visceral fat content in women. Eur Arch Psychiatry Clin Neurosci. 2011;261(8):551–7.

86. Weber-Hamann B, Werner M, Hentschel F, Bindeballe N, Lederbogen F, Deuschle M, et al. Metabolic changes in elderly patients with major depression: Evidence for increased accumulation of visceral fat at follow-up. Psychoneuroendocrinology. 2006 Apr;31(3):347–54.

87. Kim NH, Kim HS, Eun CR, Seo JA, Cho HJ, Kim SG, et al. Depression Is Associated with Sarcopenia, Not Central Obesity, in Elderly Korean Men. J Am Geriatr Soc. 2011 Nov 22;59(11):2062–8.

88. Krishnamurthy P, Romagni P, Torvik S, Gold P, Charney D, Detera-Wadleigh S, et al. Glucocorticoid Receptor Gene Polymorphisms in Premenopausal Women with Major Depression. Horm Metab Res. 2008 Mar 4;40(3):194–8.

89. Alexopoulos N, Katritsis D, Raggi P. Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis. Atherosclerosis. 2014;233(1):104–12.

90. Ma X, Lee P, Chisholm DJ, James DE. Control of adipocyte differentiation in different fat depots; implications for pathophysiology or therapy. Front Endocrinol (Lausanne). 2015 Jan;6:1.

91. Fontana A, Spadaro S, Copetti M, Spoto B, Salvemini L, Pizzini P, et al. Association between Resistin Levels and All-Cause and Cardiovascular Mortality: A New Study and a Systematic Review and Meta-Analysis. PLoS One. 2015 Jan;10(3):e0120419.

92. Després J-P. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012 Sep 4;126(10):1301–13.

93. Blüher M. The distinction of metabolically “healthy” from “unhealthy” obese individuals. Curr Opin Lipidol. 2010 Feb;21(1):38–43.

94. Rebuffé-Scrive M, Walsh UA, McEwen B, Rodin J. Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. Physiol Behav. 1992 Sep;52(3):583–90.

95. Golden SH, Malhotra S, Wand GS, Brancati FL, Ford D, Horton K. Adrenal gland volume and dexamethasone-suppressed cortisol correlate with total daily salivary cortisol in African-American women. J Clin Endocrinol Metab. 2007;92(February):1358–63.

96. Kessing LV, Willer IS, Knorr U. Volume of the adrenal and pituitary glands in depression. Psychoneuroendocrinology. 2011;36(1):19–27.

97. Eskandari F, Mistry S, Martinez PE, Torvik S, Kotila C, Sebring N, et al. Younger, premenopausal women with major depressive disorder have more abdominal fat and increased serum levels of prothrombotic factors: Implications for greater cardiovascular risk. Metabolism. 2005;54:918–24.

98. Everson-Rose SA, Lewis TT, Karavolos K, Dugan SA, Wesley D, Powell LH. Depressive symptoms and increased visceral fat in middle-aged women. Psychosom Med. 2009 May;71(4):410–6.

99. Weber-Hamann B, Hentschel F, Kniest A, Deuschle M, Colla M, Lederbogen F, et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. Psychosom Med. 2002;64:274–7.

100. Kahl KG, Bester M, Greggersen W, Rudolf S, Dibbelt L, Stoeckelhuber BM, et al. Visceral fat deposition and insulin sensitivity in depressed women with and without comorbid borderline personality disorder. Psychosom Med. Jan;67(3):407–12.

101. Scharnholz B, Gilles M, Marzina A, Kommer M, Lederbogen F, Wudy S a., et al. Do depressed patients without activation of the hypothalamus-pituitary-adrenal (HPA) system have metabolic disturbances? Psychoneuroendocrinology. 2014;39:104–10.

102. Kahl KG, Schweiger U, Pars K, Kunikowska A, Deuschle M, Gutberlet M, et al. Adrenal gland volume, intra-abdominal and pericardial adipose tissue in major depressive disorder. Psychoneuroendocrinology. 2015;58:1–8.

103. Wittchen H-U. Strukturiertes klinisches Interview für DSM-IV : SKID. Achse I und II : Handanweisung. Hogrefe, Verlag für Psychologie; 1997.

104. Bernhard Strauss JS. Klinische Interviews und Ratingskalen. Hogrefe Verlag; 2004.

105. Cuppett M, Latin RW. A Survey of Physical Activity Levels of Certified Athletic Trainers. J Athl Train. 2002 Sep;37(3):281–5.

106. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1832;22(140):55.

107. Medical Dictionary for the Health Professions and Nursing. Pack years [Internet]. 2012 [cited 2016 May 17]. Available from: http://medical-dictionary.thefreedictionary.com/pack+years

108. Deutsche Hauptstelle für Suchtfragen e.V. Alkohol und gesundheitliche Risiken [Internet]. 2014 [cited 2016 May 17]. p. 1–4. Available from: http://www.dhs.de/fileadmin/user_upload/pdf/Factsheets/Factsheet_Alkohol_gesundh-Risiken_2014.pdf

109. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. Circulation. 2004;109(August 2004):433–8.

110. Nemeroff CB. Adrenal Gland Enlargement in Major Depression. Arch Gen Psychiatry. 1992 May 1;49(5):384.

111. Amsterdam JD, Marinelli DL, Arger P, Winokur A. Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: A pilot study. Psychiatry Res. 1987 Jul;21(3):189–97.

112. Kim TH, Yu SH, Choi SH, Yoon JW, Kang SM, Chun EJ, et al. Pericardial fat amount

is an independent risk factor of coronary artery stenosis assessed by multidetector-row computed tomography: the Korean Atherosclerosis Study 2. Obesity (Silver Spring). 2011;19(5):1028–34.

113. Miao C, Chen S, Ding J, Liu K, Li D, Macedo R, et al. The association of pericardial fat with coronary artery plaque index at MR imaging: The Multi-Ethnic Study of Atherosclerosis (MESA). Radiology. 2011 Oct;261(1):109–15.

114. Ding J, Kritchevsky SB, Harris TB, Burke GL, Detrano RC, Szklo M, et al. The association of pericardial fat with calcified coronary plaque. Obesity (Silver Spring). 2008 Aug;16(8):1914–9.

115. Raggi P. Epicardial adipose tissue as a marker of coronary artery disease risk. J Am Coll Cardiol. 2013 May 2;61(13):1396–7.

116. Iacobellis G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nat Rev Endocrinol. 2015;11:363–71.

117. Hirata Y, Kurobe H, Akaike M, Chikugo F, Hori T, Bando Y, et al. Enhanced inflammation in epicardial fat in patients with coronary artery disease. Int Heart J. 2011 Jan;52(3):139–42.

118. Prati F, Arbustinib E, Labellarte A, Sommariva L, Pawlowski T, Manzoli A, et al. Eccentric atherosclerotic plaques with positive remodelling have a pericardial distribution: A permissive role of epicardial fat? A three-dimensional intravascular ultrasound study of left anterior descending artery lesions. Eur Heart J. 2003;24(4):329–36.

119. Ward M. The influence of plaque orientation (pericardial or myocardial) on coronary arterial remodeling. Atherosclerosis. 2001 Jan;154(1):179–83.

120. Pezeshkian M, Noori M, Najjarpour-Jabbari H, Abolfathi A, Darabi M, Darabi M, et al. Fatty acid composition of epicardial and subcutaneous human adipose tissue. Metab Syndr Relat Disord. 2009 May;7(2):125–31.

121. Zhang CL, Lyngmo V, Nordøy A. The effects of saturated fatty acids on endothelial cells. Thromb Res. 1992 Jan 1;65(1):65–75.

122. Hall JE. Pocket Companion to Guyton & Hall Textbook of Medical Physiology. Elsevier Health Sciences; 2011. 736 p.

123. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med. 2005 Oct;2(10):536–43.

124. Rosmalen JGM, Kema IP, Wüst S, van der Ley C, Visser ST, Snieder H, et al. 24 h urinary free cortisol in large-scale epidemiological studies: short-term and long-term stability and sources of variability. Psychoneuroendocrinology. 2014 Sep;47:10–6.

125. Wass JAH, Stewart PM. Oxford Textbook of Endocrinology and Diabetes. Oxford University Press; 2011.

126. Remer T, Maser-Gluth C, Wudy S a. Glucocorticoid measurements in health and disease--metabolic implications and the potential of 24-h urine analyses. [Internet]. Vol. 8, Mini reviews in medicinal chemistry. 2008 [cited 2015 Apr 18]. p. 153–70. Available from: http://www.eurekaselect.com/82187/article

127. Raff H, Raff JL, Findling JW. Late-night salivary cortisol as a screening test for Cushing's syndrome. J Clin Endocrinol Metab. 1998 Aug;83(8):2681–6.

128. Trilck M, Flitsch J, Lüdecke DK, Jung R, Petersenn S. Salivary cortisol measurement--a reliable method for the diagnosis of Cushing's syndrome. Exp Clin Endocrinol Diabetes. 2005 May;113(4):225–30.

129. Nemeroff CB, Vale WW. The neurobiology of depression: Inroads to treatment and new drug discovery. J Clin Psychiatry. 2005;66(suppl 7):5–13.

130. Imaki T, Naruse M, Takano K. Adrenocortical hyperplasia associated with ACTH-dependent Cushing's syndrome: comparison of the size of adrenal glands with clinical and endocrinological data. Endocr J. 2004 Feb;51(1):89–95.

131. Rubin RT, Phillips JJ. Adrenal gland volume determination by computed tomography and magnetic resonance imaging in normal subjects. Vol. 26, Investigative radiology. 1991. p. 465–9.

132. Freel EM, Nicholas RS, Sudarshan T, Priba L, Gandy SJ, McMillan N, et al. Assessment of the accuracy and reproducibility of adrenal volume measurements using MRI and its relationship with corticosteroid phenotype: A normal volunteer pilot study. Clin Endocrinol (Oxf). 2013;79(4):484–90.

133. Grant L a, Napolitano A, Miller S, Stephens K, McHugh SM, Dixon AK. A pilot study to assess the feasibility of measurement of adrenal gland volume by magnetic resonance imaging. Acta radiol. 2010;51(1):117–20.

134. Iacobellis G, Petramala L, Barbaro G, Kargi AY, Serra V, Zinnamosca L, et al. Epicardial fat thickness and left ventricular mass in subjects with adrenal incidentaloma. Endocrine. 2013;44:532–6.

135. Debono M, Prema A, Hughes TJB, Bull M, Ross RJ, Newell-Price J. Visceral fat accumulation and postdexamethasone serum cortisol levels in patients with adrenal incidentaloma. J Clin Endocrinol Metab. 2013 Jun 30;98(6):2383–91.

136. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009 Feb;71(2):171–86.

137. Kahl KG, Herrmann J, Stubbs B, Kr??ger THC, Cordes J, Deuschle M, et al. Pericardial adipose tissue and the metabolic syndrome is increased in patients with chronic major depressive disorder compared to acute depression and controls. Prog Neuro-Psychopharmacology Biol Psychiatry. 2017;72:30–5.

138. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry. 2010 Oct 15;71(10):1259–72.

139. Laimer M, Kramer-Reinstadler K, Rauchenzauner M, Lechner-Schoner T, Strauss R, Engl J, et al. Effect of Mirtazapine Treatment on Body Composition and Metabolism. J Clin Psychiatry. 2006 Mar 15;67(3):421–4.

140. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. Psychosom Med. Jan;66(4):466–74.

141. Banankhah SK, Friedmann E, Thomas S. Effective treatment of depression

improves post-myocardial infarction survival. World J Cardiol. 2015 May 26;7(4):215–23.

142. Glassman AH. Sertraline Treatment of Major Depression in Patients With Acute MI or Unstable Angina. JAMA. 2002 Aug 14;288(6):701.

143. Zuidersma M, Conradi HJ, van Melle JP, Ormel J, de Jonge P. Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: a randomized controlled trial. J Psychosom Res. 2013 Jan;74(1):25–30.

144. Shapiro PA. Depression treatment and coronary artery disease outcomes: time for reflection. J Psychosom Res. 2013 Jan;74(1):4–5.

145. Guthrie B, Thompson A, Dumbreck S, Flynn A, Alderson P, Nairn M, et al. HEALTH SERVICES AND DELIVERY RESEARCH Better guidelines for better care: accounting for multimorbidity in clinical guidelines – structured examination of exemplar guidelines and health economic modelling. 2017;2050–4349.

146. Iacobellis G, Willens HJ, Cobelli F De, Esposito A, Belloni E, Natali G, et al. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr. 2009 Dec 1;22(12):1311-9; quiz 1417-8.

147. Willens HJ, Byers P, Chirinos JA, Labrador E, Hare JM, de Marchena E, et al. Effects of weight loss after bariatric surgery on epicardial fat measured using echocardiography. Am J Cardiol. 2007 May 1;99(9):1242–5.

148. Iacobellis G, Singh N, Wharton S, Sharma AM. Substantial Changes in Epicardial Fat Thickness After Weight Loss in Severely Obese Subjects. Obesity. 2008 Jul;16(7):1693–7.

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Dissertation

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in Vorbereitung	*Liver Function Assessment Using Indocyanine Green* *Plasma Disappearance Rate in a Young Male with Icteric Leptospirosis* Kunikowska AJ, Huber W
in Vorbereitung	*Enigmatic Calvin Cycle of Chemosynthetic Symbionts Deciphered* Dmytrenko O, Kunikowska AJ, Cavanaugh CM
2015	*Adrenal Gland Volume, Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder* Kahl KG, Schweiger U, Pars K, Kunikowska A, Deuschle M, Gutberlet M, et al. Psychoneuroendocrinology. 2015;58:1–8

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Hannover, Juni 2018

ERKLÄRUNG NACH § 2 ABS. 2 Nr. 6 und 7 der PromO

Ich erkläre, dass ich die der Medizinischen Hochschule Hannover zur Promotion eigereichte Dissertation mit dem Titel Adrenal Gland Volume and its Association with Intra-abdominal and Pericardial Adipose Tissue in Major Depressive Disorder in der Klinik für Psychiatrie, Sozialpsychiatrie und Psychotherapie unter Betreuung von Prof. Dr. med Kai G. Kahl and Ko-Betreuung von PD. Dr. med. Dagmar Hartung ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

Die Gelegenheit zum vorliegenden Promotionsverfahren ist mir nicht kommerziell vermittelt worden. Insbesondere habe ich keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen und Betreuer für die Anfertigung von Dissertationen sucht oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt. Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Weiterhin versichere ich, dass ich den beantragten Titel bisher noch nicht erworben habe.

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