Evidence Linking Mental Health with Obesity and Metabolic Syndrome: The Role of Inflammation

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Abstract The prevalence of the metabolic syndrome has risen rapidly within the background of the global obesity epidemic, and estimates suggest that this number may continue to rise. A chronic low-grade inflammatory state is associated with the presence of the metabolic syndrome, reflecting increased production of proinflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), as well as the adipokines leptin and adiponectin. Inflammation is being increasingly recognized as a mechanism that may contribute to the pathogenesis of mental health disorders, because it has been documented that peripheral hormonal and inflammatory signals can access the brain and activate relevant cell types that serve to amplify central inflammatory responses. Inflammation related to obesity may be the mechanism underlying the association between metabolic syndrome and mental health disorders.

Keywords Depression · Anxiety · Schizophrenia · Inflammation · Obesity · Metabolic syndrome

Introduction

The prevalence of the metabolic syndrome (MetS) has risen rapidly within the background of the global obesity epidemic. It is estimated that as many as 36 % of U.S. adults are overweight or obese [1], whereas 34 % of U.S. adults meet criteria for MetS [2]. A number of guidelines have been

published that define the criteria for the diagnosis of MetS; however, the most widely used come from the 2001 Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III), because it employs easily measurable risk factors [3]. The guidelines have been revised since the original report for stricter criteria [4] and currently include having three or more of the following five cardiovascular disease (CVD) risk factors: 1) central obesity (waist circumference: men ≥ 102 cm; women ≥ 88 cm); 2) elevated triglycerides (≥ 150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men < 40 mg/dl; women < 50 mg/dl); 4) systemic hypertension ($\geq 130/\geq 85$ mm Hg); and 5) elevated fasting glucose (≥ 100 mg/dl). MetS is widely recognized for its association with increased CVD morbidity and mortality [5•, 6]; however, its association with disorders of mental health is being increasingly documented. Numerous reports have confirmed that persons with mental illness have an increased prevalence of cardiometabolic risk factors that adversely impact CVD morbidity and mortality, and in some cases, treatment with psychotropic medications can actually increase that risk.

Central or abdominal obesity is considered to be the most prevalent manifestation of MetS and is of central importance in the clinical diagnosis, because it is a marker of “dysfunctional adipose tissue.” [7] Adipose tissue is now recognized as an endocrine organ that secretes numerous immunomodulatory factors. Abdominal adiposity can be further characterized by excess visceral (VAT) and subcutaneous (SAT) adipose tissues, which likely differ in their metabolic activity and functional consequences, as VAT seems to be a significant source of inflammatory signals related to macrophage infiltration into adipose tissue [8, 9]. For any given amount of total body fat, individuals with a selective excess of VAT are at substantially higher risk of being characterized by insulin resistance and the features of the MetS [7, 10]. Recent data suggest that in obese individuals, VAT is more closely

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associated with an adverse metabolic, dyslipidemic, and atherogenic profile, whereas SAT demonstrates a more benign phenotype characterized by modest associations with inflammatory biomarkers, but no association with dyslipidemia, insulin resistance, or atherosclerosis [11•].

A chronic low-grade inflammatory state is associated with the presence of the MetS, reflecting increased production of the acute phase reactant C-reactive protein (CRP), and proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) among others. CRP is the most well-recognized biomarker of systemic inflammation, because it enhances traditional prognostic information for CVD risk and outcomes in patients with MetS [12, 13]. The contribution of IL-6 and TNF- α to atherogenic processes is less well understood than the role of CRP. However, multiple studies have shown that IL-6 and TNF- α are associated with incident CVD and mortality [14, 15] and enhance risk prediction for total CVD mortality in addition to traditional risk factors and CRP [16•].

Levels of CRP, IL-6, and TNF- α are increased in persons with MetS [13, 17, 18] and may contribute to the excess CVD risk in this population. The low-grade inflammatory state that characterizes MetS is attributed to the increased activity of macrophages in the adipose tissue of obese individuals [19]. Macrophages increase in number in the adipose tissue of obese individuals, and these macrophages are responsible for most of the cytokine production in obese adipose tissue. In fact, these macrophages account for most of the obesity-associated TNF- α and significant amounts of IL-6 secreted from the adipose tissue of obese individuals. The increased production of TNF- α and IL-6 in obese adipose tissue, in addition to other proinflammatory cytokines, further induces CRP secretion from the liver and stimulates the hypothalamic-pituitary-adrenal (HPA) axis, leading to a vicious cycle of worsened central obesity, hypertension, and insulin resistance [20].

Adipose tissue also secretes a number of bioactive peptides termed “adipokines,” which play a central role in energy and vascular homeostasis, as well as immunity. With increasing adiposity, the proinflammatory adipokine leptin is overproduced promoting insulin resistance and other metabolic abnormalities, while the anti-inflammatory and insulin-sensitizing adipokine adiponectin is decreased [21]. Leptin levels are higher in obese individuals, partly due to overproduction, and partly due to leptin resistance in a similar way that patients with type 2 diabetes are resistant to insulin [22•, 23]. Leptin has direct proinflammatory effects and is known to activate circulating monocytes in addition to upregulating *in vivo* production of IL-6 and TNF- α [24]. Adiponectin exerts beneficial cardioprotective effects at every stage of the atherosclerotic process, including suppression of vascular-smooth muscle cell proliferation and migration and inhibition of macrophage-to-foam cell transformation [25].

Adiponectin also has potent anti-inflammatory and antioxidant properties, including inhibition of TNF- α -induced superoxide radical generation in endothelial cells [26].

Systemic inflammation is increasingly implicated in the pathogenesis of neuropsychiatric disorders. Inflammatory molecules and cells are fundamental to the maintenance of central nervous system (CNS) and neuronal integrity but also can be destructive when the inflammatory response is overactive or sustained [27••]. Peripheral inflammatory cytokines, such as those circulating as part of the MetS, may induce loss of integrity of the blood–brain barrier (BBB) and gain access to the CNS via leaky regions around endothelial cell tight junctions, allowing transport of peripheral inflammatory signals into the brain [28]. Obesity and MetS are both highly prevalent in patients with neuropsychiatric disorders, such as depression, anxiety, and schizophrenia. However, it is not clear whether this association is due to behaviors in patients with mental illness that promote weight gain, or whether the inflammation related to obesity further promotes the symptoms of mental illness. However, increasing data confirm that chronic immune activation contributes to the immense burden of neuropsychiatric disorders, and obesity-related inflammation may provide a link between MetS and mental illness. In this review, we examine the pertinent literature that explores the inflammatory link between mental health and obesity in the MetS.

Depression

Depression is one of the most common psychiatric illnesses in the world. It is estimated that 1 in 5 U.S. adults have at least one episode of major depression in their lifetime, and that depression is the leading cause of disability in the U.S. for adults aged 15 to 44 years [29, 30]. Depression and obesity share overlapping psychosocial and pathophysiological etiologies, and an association between the two conditions has been seen in many population-based studies [22••, 31•, 32••]. Studies have also shown a higher prevalence of depression in patients with MetS [33–35, 36•], and it has been postulated that obesity-related inflammation may be the underlying link. For instance, depressive symptoms and MetS were analyzed in 652 women in the Women's Ischemia Syndrome Evaluation (WISE) study [37]. After adjusting for demographic factors, lifestyle and functional status, depressive symptoms were associated with ~60 % increased odds for MetS compared with no depression. Furthermore, women with depressive symptoms had 2.6 times higher risk of CVD over a median follow-up of 5.9 years. However, adding MetS to the multivariable analysis only decreased the risk of CVD associated with depression by 7 %, showing that MetS does not fully explain the association between depression and risk of CVD. Other epidemiologic cohort studies have investigated whether

there is a bidirectional association between depression and MetS. A recent meta-analysis that included 9 studies ($N=26,936$ with 2,316 new-onset depression case subjects) reported an adjusted OR 1.49 [1.19–1.87] with depression as the outcome, and 4 studies ($N=3,834$ with 350 MetS case subjects) reported an adjusted OR 1.52 [1.2–1.91] with MetS as the outcome [38]. These results support the concept of a bidirectional association between depression and MetS.

Major depression involves complex interactions between genes and the environment that converge in the brain [39, 40]. Numerous mechanisms have been implicated, including dysfunction of monoaminergic systems [41] and dysregulation of the HPA axis [42, 43]. Inflammatory biomarkers and cytokines have been shown to influence many of these pathways [44]. Of the biomarkers that have been examined in depressed individuals, CRP and IL-6 are the most extensively studied. Numerous analyses have reported higher levels of CRP [31•, 44, 45•, 46–49] in individuals with depressive symptoms. Furthermore, several reports have shown that the association between CRP and depression differs based on gender and race/ethnicity [47, 48, 50, 51•, 52•], as well as the subtype of depressive symptoms [45•, 53]. For instance, our analysis of 512 participants in the Morehouse and Emory Team up to Eliminate Health Disparities (META-Health) Study showed white women with mild to severe depressive symptoms had higher levels of CRP compared with those with minimal to no depressive symptoms [52•]. However, there were no differences in levels of CRP by severity of depressive symptoms in white men or African Americans of either sex. Studies also have confirmed an association between higher levels of IL-6 and depressive symptoms [49, 54–57]. Similar to CRP, a recent meta-analysis confirmed that the association of IL-6 and depression is influenced by gender and obesity [58]. The meta-analysis found that very few studies provided data partitioned by gender, but the relationship between IL-6 and depression was significant for those samples comprised only of women ($n=13$), whereas there was no association in those samples comprised only of men. There may be a genetic component to the association of IL-6 levels and depressive symptoms. Analyses of 188 male twins from the Vietnam Era Twin Registry found a significant correlation between IL-6 and depressive symptoms, and after adjustment for other risk factors, genetic factors accounted for approximately 93 % of the covariation between depressive symptoms and IL-6 [54].

The association of TNF- α with depressive symptoms has not been as clearly defined as with other biomarkers. A few analyses have noted higher levels of TNF- α in depressed subjects [36•, 59•], whereas others have shown no association [33, 60]. A recent meta-analysis of 13 studies confirmed significantly higher concentrations of TNF- α in depressed subjects compared with controls [61•]. Similar to findings with CRP, reports have shown that the association between TNF- α and depression may differ based on the subtype of

depressive symptoms [36•]. Furthermore, recent trials using the TNF- α antagonist infliximab to reduce depressive symptoms in patients with treatment-resistant depression determined that baseline concentrations of TNF- α and its soluble receptors were significantly higher in infliximab-treated responders compared to nonresponders [62••]. To date, relatively few studies have examined levels of TNF- α in depressed subjects with MetS. Capuron et al. did not note a correlation of TNF- α with depressive symptoms in 323 male twins with and without MetS [33]. Similarly, Zeugmann et al. examined 70 inpatients with major depressive disorder and did not find a relationship between MetS and TNF- α levels [63].

Fewer studies have examined the relationship between depression and the adipokines. Both low [64, 65] and high [66, 67] levels of leptin have been associated with depressive symptoms. Studies from our group found the association of depression and leptin is mediated by adiposity, with body mass index (BMI) accounting for 61 % of the variance in leptin levels [22••]. Compared with those with minimal depression, participants with moderate to severe depressive symptoms and low to normal weight had lower levels of leptin, whereas participants with moderate to severe depressive symptoms who were overweight and obese had higher levels of leptin. Our findings suggest that leptin insufficiency may occur in a subset of depressed patients, whereas the high leptin levels observed with obesity may be indicative of leptin resistance in other patients. Also similar to CRP and IL-6, the association between leptin and depression may differ based on the subtype of depressive symptoms. A recent analysis by Chirinos et al. found that leptin was significantly associated with somatic depressive symptoms, but not total or cognitive symptoms in 135 participants with the MetS [68•]. Relatively small studies have shown lower levels of adiponectin in depressed individuals [69, 70, 71•], and an analysis from Zeugmann et al. also confirmed lower levels of adiponectin in depressed patients with MetS compared with depressed patients without MetS [63]. A study of 2,359 diabetic youth noted higher levels of adiponectin, leptin, CRP in type 1 diabetic participants with greater depressive symptoms [72•]. However, none of the markers were significantly associated with depression after adjustment for demographic and clinical covariates.

Schizophrenia

Multiple large studies have estimated a prevalence of MetS in patients with schizophrenia that is two to three times higher than the general population [73, 74]. This clustering of CVD risk factors in schizophrenic patients has been attributed to unhealthy lifestyle, including poor diet, smoking, and sedentary behavior. However it also is well recognized that

antipsychotic drugs cause weight gain as an adverse side effect, further increasing the risk of obesity related illnesses, such as diabetes and unfavorable lipid profile. In fact, a recent study of MetS in patients with schizophrenia showed that the incidence of new cases of MetS after three years in those started on second-generation antipsychotics was over twice the incidence of those treated with first-generation antipsychotic agents (27.8 % vs. 13.1 %). Moreover, in patients without MetS at baseline, the risk of developing MetS was 3.6-fold greater in patients started on second-generation antipsychotics [75]. Because of the high prevalence of CVD risk factors, and an even higher incidence of developing MetS after starting antipsychotic medications, consensus guidelines recommend appropriate baseline metabolic screening for patients treated with second-generation antipsychotics and ongoing monitoring of parameters, including blood pressure, height and weight to calculate BMI, waist circumference, and fasting plasma lipids and glucose [76].

There has been considerable interest in the contribution of proinflammatory cytokines to the neuropathogenesis of schizophrenia. Uncontrolled activity of proinflammatory cytokines, biomarkers, and microglia, resident macrophages that act as the first and main immune defense in the CNS, can induce schizophrenia in patients with underlying genetic vulnerability [77]. Elevated levels of CRP have been observed in multiple observational and longitudinal studies, and a recent meta-analysis confirms a prevalence of elevated CRP in 28 % of patients with schizophrenia and related disorders [78]. Furthermore, the relationship between CRP and schizophrenia has remained significant even after controlling for important confounding CVD risk factors, such as age, BMI, and smoking status [79]. Multiple small studies have shown higher levels of IL-6 in the serum as well as the CSF in schizophrenic patients compared with healthy controls [80, 81]. In addition, specific investigations have revealed a relationship between various IL-6 gene polymorphisms and higher IL-6 blood levels in patients with schizophrenia [80, 82]. A recent meta-analysis confirmed that levels of TNF- α are elevated in acute exacerbations of schizophrenia and remain elevated following antipsychotic treatment [83].

There has been considerable interest in the association of schizophrenia with the adipokines given the high incidence of adverse effects that antipsychotic medications have on food intake, weight gain, and other metabolic parameters. Analyses have shown higher levels of leptin in schizophrenic patients with MetS compared with healthy controls [84], and polymorphisms in the leptin gene are thought to contribute to antipsychotic-induced weight gain [85, 86]. Most studies have shown adiponectin levels to be lower in schizophrenic patients with MetS compared with healthy controls or schizophrenic patients without MetS [87–89], although other studies have shown higher levels of adiponectin [84]. However, there may be a significant effect of antipsychotic treatment, as lower

levels of adiponectin and weight gain after taking atypical antipsychotics are associated with higher risk of MetS [89].

Several studies have investigated the effects of antipsychotics on inflammation; however, the results have been inconsistent largely because the anti-inflammatory effects of antipsychotics may vary based on whether the drug is a typical or atypical antipsychotic. For instance, typical antipsychotic drugs, such as haloperidol and perazine, decrease pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α) in patients with schizophrenia [90]. However, atypical antipsychotics, such as clozapine, are associated with enhanced inflammatory responses [91, 92]. Additionally, in a post-hoc analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the atypical antipsychotic olanzapine significantly enhanced C-reactive protein (CRP) levels after 18 months of treatment [93].

Anxiety

The relationship between anxiety and MetS has not been clearly established. Multiple cross-sectional studies found no relationship between anxiety symptoms and MetS [94–97]. Longitudinal studies have yielded conflicting results. A small longitudinal study of Finnish women showed that the presence of MetS at baseline predicted the development of anxiety symptoms during a follow-up period of 7 years [98]. However, the presence of anxiety symptoms at baseline did not predict the development of MetS during the study period. Results from the Women's Ischemia Syndrome Evaluation Study also did not find an association between anxiety symptoms and MetS [99].

An even smaller number of studies have examined the relationship between anxiety and proinflammatory biomarkers or adipokines. Liukkonen et al. examined whether anxiety symptoms were associated with low-grade inflammation in a Finnish population [100]. After adjusting for confounders, anxiety symptoms increased the probability for elevated CRP levels in males more than 2-fold, whereas comorbid anxiety and depressive symptoms caused a 1.7-fold increase in the probability for elevated CRP levels. A recent analysis from the Netherlands Study of Depression and Anxiety found elevated levels of CRP in men, but not in women, with a current anxiety disorder compared with controls; there was no association of anxiety with IL-6 or TNF- α [101]. Pitsavos et al. found a positive correlation between anxiety symptoms and levels of CRP, IL-6 and TNF- α in Greek men, and a positive correlation between anxiety symptoms and levels of CRP in women [102]. A U.S. study also found an association of anxiety symptoms with elevated CRP; however, these associations were attenuated after adjusting for demographic and health-related covariates [103].

Finally, few studies have examined the association of inflammatory biomarkers or adipokines with anxiety in the setting of obesity or MetS. Capuron et al. examined the relationship between adiposity, inflammation, and emotional status in obese women awaiting gastric surgery. The authors found that IL-6 and CRP levels were strongly associated with anxiety symptoms in obese participants, even after controlling for BMI; however, leptin levels were not associated with anxiety symptoms in this cohort [104]. Higher levels of phobic anxiety were associated with higher leptin and TNF- α levels in 984 women with type 2 diabetes from the Nurses' Health Study; however, there was no association with adiponectin [105]. Further research is needed to examine the relationship of inflammation with anxiety symptoms in subjects with MetS.

Conclusions

Considerable data suggest that individuals with neuropsychiatric disorders tend to have excess CVD morbidity and mortality, largely due to high rates of smoking, central obesity, and diabetes mellitus. Furthermore, the use of certain psychotropic drugs worsens these metabolic disorders, further exacerbating obesity, dyslipidemia, glucose intolerance, and the MetS. To date, it remains unclear whether the chronic inflammation associated with the underlying metabolic abnormalities predisposes to mental illness, or whether chronic inflammation associated with mental illness leads to lifestyles that then predispose to excess CVD morbidity. Regardless, persons with certain psychiatric illnesses are at such high risk for CVD that screening for traditional risk factors, such as waist circumference, blood pressure, and plasma glucose, is currently recommended. Although additional screening using proinflammatory biomarkers, cytokines, and adipokines is not currently standard of care, there is growing evidence that these molecules provide important information regarding severity of both metabolic as well as psychiatric illness, particularly in obese individuals. It is not unreasonable to think that future screening recommendations might incorporate inflammatory biomarkers for complete assessment of a patient's metabolic and psychiatric risk.

Compliance with Ethics Guidelines

Conflict of Interest Alanna A. Morris declares that she has no conflict of interest.

Viola Vaccarino declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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