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Depressive symptoms and adipokines in women: Study of women's health across the nation

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ABSTRACT

Small clinical studies suggest depression is associated with alterations in adiponectin and leptin, adipocyte-derived secretory proteins involved in metabolic regulation; however, longitudinal data on these association are lacking. This study examined cross-sectional and longitudinal associations of depressive symptoms and major depressive disorder (MDD) with adiponectin and leptin in healthy middle-aged women (mean (SD) age, 45.6 (2.5) years). Cross-sectional analyses included 575 women with baseline adipokine data; longitudinal analyses included 262 women with 2–4 adipokine measurements over 5 years. The 20-item Center for Epidemiologic Studies Depression scale (CES-D) was used to assess depressive symptoms; history of MDD was determined by the Structured Clinical Interview for DSM-IV. Adipokines were assayed from stored serum specimens; values were log-transformed for analyses. Linear and repeated measure random effects regression models evaluated associations of baseline CES-D scores with baseline adipokine concentrations and changes over time, respectively. Secondary analyses evaluated the relation of MDD history with adipokine concentrations. Mean (SD) baseline concentrations of adiponectin and leptin were 9.90 (4.92) μg/mL and 27.02 (20.06) ng/mL; both increased over time ($p < .0001$). CES-D scores were associated with lower adiponectin at baseline (per 1-SD: estimate = -0.04, SE = .02, $p = .03$) and over time (per 1-SD: estimate = -0.055, SE = .024, $p = .02$). Associations were unchanged in risk factor-adjusted models. Women with elevated CES-D scores (≥16) had 6.9% (95% CI: −1.1%, 14.3%; $p = .089$) lower median adiponectin at baseline and 11.5% (95% CI: 1.5%, 20.4%, $p = .025$) lower median adiponectin over time in adjusted models, compared to women with CES-D < 16. Rate of change in adipokines did not vary by baseline depressive symptoms or MDD history. Depressive symptoms and MDD history were unrelated to leptin.

In women at midlife, depressive symptoms are associated with lower adiponectin, a critical anti-inflammatory biomarker involved in metabolic and cardiovascular conditions.

1. Introduction

Major depressive disorder (MDD) and depressive symptoms have been linked to obesity, metabolic syndrome, insulin resistance, and diabetes (Everson et al., 2002; Everson-Rose et al., 2004; Golden et al., 2004), all of which are metabolic risk factors that increase risk for cardiovascular disease (CVD). A potential pathophysiologic pathway by which depression influences metabolic dysregulation is inflammation (Stewart et al., 2009; Rethorst et al., 2014). Clear associations have been reported between depression and C-reactive protein (CRP), interleukin 6 (IL-6), fibrinogen, and tumor necrosis factor alpha (TNF-a) (Maes, 1999; Miller et al., 2002; Matthews et al., 2007). Negative studies exist (Steptoe et al., 2003), but on balance, data accumulating over the last two decades support this association (Raison et al., 2006; Messay et al., 2012). Nonetheless, few studies specifically have examined associations of depression with adipokines, secretory proteins

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derived from adipocytes (fat cells) that may be pro- or anti-inflammatory, and which are importantly involved in metabolic dysregulation and atherogenesis in humans (Mattu and Randeva, 2013). As described below, adiponectin and leptin are two particular adipokines of interest that may relate to both depression and CVD risk.

Adiponectin, an abundant bioactive protein secreted primarily by adipocytes, has documented anti-thrombotic, anti-inflammatory, insulin-sensitizing, and anti-atherogenic effects (Lihn et al., 2005; Mattu and Randeva, 2013). Adiponectin concentrations are inversely related to obesity, diabetes, insulin resistance, and impaired fasting glucose in cross-sectional and longitudinal studies (Yamamoto et al., 2004; Snijder et al., 2006). Lower concentrations of adiponectin are associated with greater coronary and carotid atherosclerosis (Hasan-Ali et al., 2011; Shanker et al., 2012), and increased risk of adverse cardiovascular events (Persson et al., 2010; Li et al., 2012). However, several studies have reported a seemingly paradoxical association of high adiponectin with poorer outcomes (Beatty et al., 2012; Sook Lee et al., 2013) particularly in persons with existing cardiovascular disease.

Leptin, secreted by adipocytes proportionately to body fat stores, is pro-inflammatory, pro-thrombotic, and intimately involved in metabolic regulation, energy balance, and autonomic nervous system functioning (Mattu and Randeva, 2013). Elevated leptin concentrations are related to increased carotid artery intimal-medial thickening (Ciccone et al., 2001), greater coronary calcification and incident ischemic heart disease in patients with type 2 diabetes (Vavruch et al., 2015). Leptin is associated with more adverse cardiovascular (CV) risk profiles (Shanker et al., 2012) and increased risk of CV events in cardiac patients (Wolk et al., 2004), though conflicting findings have been reported (Ku et al., 2011; Martin et al., 2015).

The relationship of these adipokines to depression has not been well studied, despite what is known about the interrelationships of inflammatory processes, depression, and cardiometabolic function and the biologic plausibility of the association (Taylor and Macqueen, 2010). Available evidence is suggestive, though not consistent (Hu et al., 2015). For example, lower adiponectin concentrations were reported in patients with major depressive disorder (MDD) or other depressive disorder compared with controls (Cizza et al., 2010; Diniz et al., 2012). In contrast, adiponectin was not associated with depression subtypes in a case-control study of young men (Su et al., 2011) and was positively related to subsyndromal depression in men but not women in a small study of elderly adults (Jeong et al., 2012). Some studies have reported higher leptin concentrations among depressed patients relative to healthy controls (Antonijevic et al., 1998; Gecici et al., 2005), but others have reported no difference (Deuschle et al., 1996; Atmaca et al., 2002). One study reported lower leptin concentrations in female patients with either major depressive disorder or schizophrenia, compared with healthy controls (Kraus et al., 2001). Common to nearly all of these studies is a focus on patient samples of limited size, which might account for some of the variation in findings. Moreover, longitudinal data on the relation of these important adipokines and depression are lacking.

These gaps in the literature are addressed by the study reported herein. We used five years of data from a community-based sample of middle-aged African-American and Caucasian women to examine cross-sectional and longitudinal associations of depressive symptoms and MDD with adiponectin and leptin. We hypothesized that women who reported more depressive symptoms and women with a lifetime history of MDD would have lower concentrations of adiponectin and higher concentrations of leptin at baseline and would experience greater changes in these adipokines over time, compared to women with fewer depressive symptoms and women without a history of MDD.

2. Methods and materials

2.1. Sample

This study uses data from the Study of Women's Health Across the Nation (SWAN), an ongoing community-based longitudinal study of the menopausal transition conducted at 7 clinical sites in the U.S. (Chicago, IL; Pittsburgh, PA; Boston, MA; Detroit, MI; Newark, NJ; Oakland, CA; Los Angeles, CA). SWAN enrolled 3302 women in 1996–97 with follow-up visits, scheduled at approximately 12- to 18-month intervals, ongoing. Eligibility criteria for SWAN included: aged 42–52 years, intact uterus, at least 1 ovary, reported menstrual bleeding and no use of reproductive hormones that affect ovarian or pituitary function within the past 3 months, not currently pregnant or breast-feeding, and self-identification as 1 of 5 pre-specified racial/ethnic groups depending on site: non-Hispanic Caucasian (all sites), African-American (Chicago, Pittsburgh, Boston, Detroit); Hispanic (Newark); Chinese or Chinese-American (Oakland); and Japanese or Japanese-American (Los Angeles). Recruitment and study design details have been reported (Sowers et al., 2000). This study also uses data on the participant's psychiatric history that was collected through an ancillary study (SWAN Mental Health Study), that was conducted within 2–9 months of the parent SWAN baseline at 3 SWAN clinical sites (Pittsburgh, PA; Chicago, IL; Newark, NJ). All women eligible for the parent SWAN study at these sites were eligible for the Mental Health Study. All participants in the parent SWAN study and ancillary SWAN Mental Health Study provided written, informed consent at each study visit. The Institutional Review Board (IRB) at each site approved the study protocols; the IRB at the University of Minnesota approved the present study.

Due to early retention problems at the Newark, NJ site, the sample for this study is limited to the participants from the Pittsburgh and Chicago sites, excluding 6 women with no available adipokine data (N = 575). Due to limited resources for the adipokine assays, we opted to design the longitudinal portion of our study to include only women without a history of CVD, diabetes or metabolic syndrome at baseline. From this healthy subset, we included all women who had a lifetime history of major depressive disorder (MDD; n = 133), determined by the Structured Clinical Interview for DSM-III-R (SCID) from the SWAN Mental Health baseline study, and an equal number of race- and age-matched (within a 5-year window) women without a history of MDD; 4 women without available adipokine data were excluded, leaving an analytic sample of 262 for longitudinal analyses.

2.2. Measures

2.2.1. Depression

Depressive symptoms were measured in the parent SWAN study at baseline with the 20-item Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977), a well-validated measure with established reliability in racially/ethnically diverse samples (Roberts, 1980) and widely used in epidemiologic studies. Lifetime history of MDD was assessed by the Structured Clinical Interview for DSM-IV (SCID), which was administered as part of the SWAN Mental Health study baseline visit.

2.2.2. Adipokines

Leptin and adiponectin were assessed in serum specimens obtained as part of the SWAN assessments at baseline for our baseline cohort, and additionally at three follow-up visits (years 01, 03 and 05) for our longitudinal cohort. Fasting morning (before 10 a.m.) blood draws were obtained for all SWAN participants. Blood draws were targeted to the early follicular phase of the menstrual cycle (days 2–5) among cycling women; among non-cycling women, blood draws are obtained within 90 days of the anniversary of their baseline SWAN study visit. Cycle day of blood draw was recorded as within or outside the targeted early follicular phase for cycling women and as outside this window for non-