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Depressive Symptoms and Metabolic Syndrome: Is Inflammation the Underlying Link?

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Abstract

Background—Behavioral alterations, including depression, are frequent in individuals with the metabolic syndrome (MetS). Recent findings suggest that chronic activation of innate immunity may be involved. The objective of this study was to examine the relationship between MetS and depressive symptoms and to elucidate the involvement of inflammation in this relationship.

Methods—Participants were 323 male twins, with and without MetS and free of symptomatic cardiovascular disease, drawn from the Vietnam-Era-Twin Registry. Depressive symptoms were measured with the Beck-Depression-Inventory (BDI). Inflammatory status was assessed using C-reactive protein (CRP) and interleukin-6 (IL-6); twins with both CRP and IL-6 levels above the median were classified as having an elevated inflammatory status. Factor analysis was performed on individual BDI items to extract specific symptom dimensions (neurovegetative, mood, affective-cognitive).

Results—Subjects with MetS had more depressive symptoms than those without. Depressive symptoms with neurovegetative features were more common and more robustly associated with MetS. Both the BDI total score and each symptom subscore were associated with inflammatory biomarkers. After adjusting for age, education and smoking status, the MetS was significantly associated with the BDI total score and the neurovegetative score. After further adjusting for inflammation, the coefficient for MetS decreased somewhat, but remained statistically significant for the BDI neurovegetative subscore. When controlling for the MetS, inflammation remained significantly associated with the BDI mood subscore.

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Conclusions—The MetS is associated with higher depressive symptomatology characterized primarily by neurovegetative features. Inflammation is one determinant of depressive symptoms in individuals with MetS.

Keywords

Metabolic Syndrome; Inflammation; Cytokines; Depression; Mood

INTRODUCTION

Metabolic syndrome (MetS) affects approximately 22% of the US adult population (1). This syndrome is characterized by coexisting metabolic abnormalities including abdominal obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension. MetS is an important risk factor for type 2 diabetes and cardiovascular disease (2,3).

Inflammation is a key component of MetS (4–7) and high levels of C-reactive protein (CRP) and proinflammatory cytokines, e.g. interleukin (IL)-6 and tumor-necrosis-factor (TNF)-alpha, represent risk factors for the development of this condition (7,8). Central obesity, another element of MetS, is a major determinant of low-grade chronic inflammation (9). Growing literature indicates that adipose tissue has a unique capacity to produce and secrete inflammatory molecules, including CRP and proinflammatory cytokines (10–13). The adipose tissue contains mature adipocytes and cell types of various lineages in the stromavascular fraction, including preadipocytes, endothelial cells and macrophages (10,14). Recent findings suggest that macrophages in the adipose tissue represent, at least partially, the originating site of low-grade inflammation in MetS (10,11,15). In addition to macrophages, adipocytes are also able to produces proinflammatory cytokines (13).

Mood symptoms are frequent in patients with MetS (16,17). In a recent study conducted in 1598 subjects at risk of cardiovascular disease, MetS was associated with an increased prevalence of depression but not anxiety (18). Nevertheless, the specific kind of depressive symptoms that occur in patients with MetS, with respect to specific symptom dimensions (e.g., mood, cognitive, or neurovegetative), remains to be determined. Fatigue is frequent in medical conditions associated with the chronic activation of innate immunity such as MetS; it is possible that neurovegetative symptoms, including fatigue, represent a major component of depressive symptoms associated with MetS (19–21).

The mechanisms underlying the development of depressive symptoms in patients with MetS have not been elucidated. There are reasons to believe that inflammatory processes chronically activated in MetS could participate in mood alterations. Proinflammatory cytokines have been linked to depression in a number of reports (22–24). Moreover, in studies of the administration of the innate immune cytokine, interferon-alpha, for infectious diseases and cancer, patients develop major depression at a rate of 30–50%, depending on the dose (25,26). Cytokine treatment affects all symptom domains of the depressive syndrome, with more profound effects on neurovegetative symptoms, compared to medically-healthy depressed subjects (19).

The purpose of this study was to elucidate the involvement of inflammatory processes in the development of depressive symptoms in individuals with MetS. We first characterized the specific mood-related dimensions associated with MetS, and next we assessed if inflammation mediated the relationship between depressive symptomatology, overall and its major dimensions, and MetS.

METHODS

Sample and Setting

Participants were drawn from the Twins Heart Study (THS), an investigation of psychological, behavioral and biological risk factors for subclinical cardiovascular disease in twins. Twins were members of the Vietnam-Era-Twin (VET) Registry (27); a registry composed of 7,369 middle-age male-male twin pairs both of whom served in the United States military during the Vietnam War (27).

THS participants included 360 twins from the VET Registry, born between 1946–1956 and free of symptomatic cardiovascular disease based on survey data collected in 1990 (28). About 2/3 of the sample was randomly selected from the VET Registry twins meeting these criteria, and the remaining 1/3 included twin pairs discordant for lifetime history of major depression. All twins were examined at the Emory University General-Clinical-Research-Center between March 2002 and March 2006. Of the 360 twins in the THS, 35 were excluded because of a reported history of symptomatic cardiovascular disease and two additional because of missing data. Thus, the sample for analysis included 323 twins.

Written informed consent was obtained for all participants. The study was approved by the Institutional-Review-Board of the Emory University School of Medicine.

Measures

Neuropsychiatric Assessment—Depressive symptoms were assessed using the Beck-Depression-Inventory, second edition (BDI-II) (29), a 21-item self-report questionnaire with scores ranging from 0–63. According to validation data and normative measures, a BDI score of 0–13 is considered minimal range, 14–19 is mild, 20–28 is moderate, and 29–63 is severe. The Structured Clinical Interview for DSM-IV was administered by a trained physician to assess lifetime history of major depressive disorder (MDD). Only 8 twins met criteria for current MDD.

Clinical and Laboratory Assessment—A medical history and a physical exam were obtained from all subjects. Weight and height were used to calculate body mass index (BMI). Systolic and diastolic blood pressure were measured by mercury sphygmomanometer on the right arm with the subject in sitting position after 10 minutes of rest; the average of two measurements 5-minute apart was used. Venous blood samples were drawn for the measurement of glucose and lipid profile after an overnight fast. Total triglycerides were determined by enzymatic methods (Beckman-Coulter Diagnostics, Fullerton, CA). Direct high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured with homogeneous assays (Equal Diagnostics, Exton, PA). Glucose levels were measured on the Beckman CX7 chemistry autoanalyzer. Cigarette smoking was classified into current smoker versus never/past smoker.

MetS Definition—We used the ATP-III criteria, recently revised by the American-Heart-Association and the National Heart, Lung and Blood Institute (30) to assess the presence of MetS (1). According to these criteria, MetS is defined by the coexistence of 3 or more of the following characteristics: 1) abdominal obesity - waist circumference >102 cm, 2) hypertriglyceridemia ≥150 mg/dL or 1.69 mmol/L, 3) low HDL cholesterol <40 mg/dL or 0.9 mmol/L, 4) high blood-pressure with ≥130/85 mm Hg, and 5) high fasting glucose ≥100 mg/dL.

Inflammatory Biomarkers—Plasma inflammatory markers were measured from fasting blood samples collected between 7:00–7:30AM the day following the neuropsychiatric

evaluations. Plasma was stored at −80°C until thawed for the measurement of high-sensitivity CRP, proinflammatory cytokines (IL-6, TNF-alpha) and their soluble receptors (sIL-6R, sTNF-RII). Plasma concentrations of inflammatory markers were assayed by quantitative enzyme-linked-immunosorbent-assay (ELISA) (R-D Systems, Minneapolis, MN) according to manufacturer's specifications. Samples were run in duplicate. Inter- and intra-assay variability is reliably <10%. CRP was measured with the Beckman-Coulter high-sensitivity CRP assay on the Synchron LX-20 analyzer. Detection limits were 0.04 pg/ml (IL-6), 0.1 pg/ml (TNF-alpha), 7 pg/ml (sIL-6R) and 1 pg/ml (sTNF-RII). Subjects were stratified based on their inflammatory status based on both CRP and IL-6 (combined inflammation) according to the strategy used earlier by other groups (31). High inflammatory status was defined as the co-existence of both high levels of CRP (≥median: 1.34 mg/L) and high levels of IL-6 (≥median: 1.66 pg/mL).

Data/Statistical Analysis—Inflammatory markers were log-transformed for statistical analysis. Factor (principal component) analysis with varimax rotations was performed on individual items of the BDI scale to extract specific symptom dimensions. Behavioral and biological data, BDI total score and subscores, were compared between participants with MetS versus participants free of MetS using generalized-estimating-equation models (GEE) to correct for the correlation of twins in each pair. The prevalence of MetS was also compared between twins with and without MDD in pairs discordant for MDD diagnosis.

Mixed regression models were performed to assess the relationship between MetS, inflammatory biomarkers and depressive symptomatology. Analyses were performed after adjusting for age, education, and current smoking status because these factors were found to be related to depression, inflammation or MetS in previous studies. Separate models were run with BDI total score and each of the subscales as dependent variables. In these models, twin pair was defined as random effect to take into account pair cluster; all p values were corrected for pair cluster. Statistical analyses were performed with SPSS-13 and SAS 9.1.

RESULTS

Characteristics of participants

The mean age of study participants was 54.3 years (SD=2.8, range=47–60). Seventy-three participants (22.6%) had a lifetime history of depression and the mean BDI score was 4.8 (SD=6.5). Forty-five percent (N=147) of participants met criteria for MetS based on the ATPIII criteria. Physical activity was lower in participants with MetS compared to those without. There was no significant difference between the two subgroups in terms of age, years of education, and current cigarette smoking (Table I). Lifetime history of MDD also did not differ according to MetS status, and similar results were obtained when the analysis was restricted to the 68 twin pairs discordant for MDD. The prevalence of MetS was 44.8% among twins without MDD and 55.1% among twins with MDD, P=0.16.

Specific dimensions of depressive symptoms and their expression in subjects with MetS versus subjects free of MetS

Principal component analysis performed on individual BDI items revealed three specific factors. The first factor (eigenvalue = 8.71) explained 41.5% of the variance and contained items addressing neurovegetative function (fatigue, loss of energy, loss of pleasure, loss of interest, indecisiveness, concentration difficulties, changes in sleeping patterns, changes in appetite, loss of interest in sex). The second factor (eigenvalue = 1.38) explained 6.6% of the variance and included items referring to mood (sadness, pessimism, suicidal thoughts, crying, agitation, irritability). Finally, the third factor (eigenvalue = 1.26) explained 6% of the variance and included affective-cognitive self-referential items referring to self-depreciation or negative

affect (self-dislike, worthlessness, self-criticism, feelings of past failure, punishment feelings, guilty feelings). Based on this 3-factor description, neurovegetative, mood and affective-cognitive subscores were calculated for each participant. Neurovegetative symptoms were more common than mood and affective-cognitive symptoms: the mean scores for each subscale were 2.90, 0.90 and 1.02, respectively.

Subjects with MetS exhibited significantly higher BDI total scores compared with those without (P=0.003), which remained significant after adjusting for age, education, and smoking status (Table II). In addition, 15% of patients with MetS exhibited depressive symptomalogy of at least moderate intensity (BDI score ≥14) in comparison with 7.4% of participants free of MetS (P=0.029). Further analyses distinguishing symptom dimensions/factors revealed that all these dimensions were associated with MetS (Table II); however, the neurovegetative symptoms were substantially more common than other symptom dimensions, and showed a more robust association than the other subscores.

Inflammatory status in subjects with and without MetS

Four participants (2 with MetS and 2 free of MetS) exhibited extreme values (<3 SD above the mean) for at least one inflammatory variable and thus were excluded from subsequent analyses on biological data. CRP, IL-6 and sTNF-RII were significantly more elevated in twins with MetS compared with those without, even after adjusting for age, education and current smoking (Table III). Complementary analyses with individual characteristics of MetS revealed that BMI, hypertriglyceridemia and low HDL cholesterol were more particularly related to inflammation (data not shown).

Depressive symptoms, inflammatory status and MetS

Both the BDI total score and symptom subscales were associated with inflammatory markers, and again CRP, IL-6 and sTNF-RII showed the highest correlations (Table IV). The associations between MetS and BDI total score, or the neurovegetative subscale score, are shown in Table V, before and after adjusting for inflammatory markers. All models adjusted for age, education and current smoking. Before adjusting for inflammation, MetS was significantly associated with the BDI total score and the neurovegetative score, but not with other subscores. The MetS remained significantly associated with the neurovegetative score after adjusting for CRP or IL-6 or combined inflammation (IL-6 and CRP), although the coefficient decreased somewhat. In the final model, inflammatory biomarkers (IL-6 and CRP) combined, controlling for MetS, were significantly associated with BDI depressed mood, with similar, albeit non-significant, relationships between combined inflammatory biomarkers with total BDI scores and other symptom subscores.

DISCUSSION

We found a strong association between depressive symptoms and the MetS. This finding is in accordance with previous data documenting an elevated prevalence of behavioral alterations, including depression, in patients with metabolic disturbances (16–18). The association between MetS and mood has not been found in all studies (32) probably due to methodological differences across studies.

Based on dimensional analyses, the present study revealed that depressive symptomatology in MetS participants was primarily related to neurovegetative features (e.g., fatigue, loss of energy, anhedonia, etc.) and less associated with mood and cognitive features. This result is important since it provides, for the first time, a better characterization of depressive symptoms in patients with MetS and may help to define more precise phenomenological and pathophysiological hypotheses for the relationship between MetS and psychopathology. There

was no significant difference between participants with MetS and participants free of MetS in terms of lifetime history of depression, suggesting that depressive symptomatology in MetS is more related to the current medical/metabolic condition of participants rather than to a personality/depressive preexisting trait. In our study, the prevalence of lifetime MDD was 22.6%. This prevalence was higher to prevalence in the general U.S. population (16.2%) (33) because twin pairs discordant for MDD were oversampled in the present investigation.

Consistent with previous reports (4,6,7), MetS participants were found to exhibit higher low-grade inflammatory state. Inflammation in MetS may originate from the adipose tissue, which contains mature adipocytes and cells types from lineages in the stromavascular fraction, including macrophages (10,11).

We found that depressive symptoms, and each symptom dimensions, were associated with inflammation. Addition of inflammatory markers to the model investigating the association of the total BDI score, or the neurovegetative score, with MetS explained some of, but not all, the association. Interestingly, inflammation was found to be independently associated with the BDI mood subscore when controlling for MetS. Thus, inflammation appears to be, in part, a mediator for the link between mood symptoms and MetS. Previous studies in subjects with other medical conditions associated with chronic activation of innate immunity, such as coronary heart disease, also showed clear associations between inflammation and depressive symptoms (34,35). Similarly, activation of inflammatory markers was found to significantly correlate with fatigue in breast cancer survivors (20). Support for an association between chronic inflammation and depressive symptoms also comes from our previous data indicating a high incidence of depressive disorders (30–50%) in medically-ill patients receiving repeated/daily injections of interferon-alpha and/or IL-2 (19,25,26,36).

A limitation of our study is the low prevalence of current MDD in participants. This limitation may contribute to the fact that mood and cognitive features of depression were less expressed than neurovegetative features in our subjects. However, neurovegetative features were shown elsewhere to precede the development of mood and cognitive symptoms in patients with chronically activated innate immunity (19), therefore supporting their unique link with chronic inflammation. Because of the low rate of MDD in our study population, analyses using this classification variable as stratifying factor (MDD versus non-depressed) were highly limited. Therefore, the relationship between MetS and mood was assessed using BDI cut-off scores. We found that 15% of patients with MetS exhibited depressive symptomatology of at least moderate intensity in comparison with 7.4% of participants free of MetS. These proportions were somewhat similar to those reported in other studies (18).

Another limitation is that, because of the cross-sectional design, we were unable to clarify the direction of the association between MetS, inflammation and depression. However, experimental studies strongly support the link between inflammatory cytokines and mood/neurovegetative disturbances consistent with depressive disorders (19,25,26,36).

In conclusion, we found that MetS is associated with depressive symptoms and that the inflammatory response characteristic of this medical condition may represent a partial determinant of the development of mood alterations.

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Table I

Characteristics of twins with and without the metabolic syndrome (MetS).

Characteristics	Presence of MetS		*P* value
	No N = 176	Yes N = 147	
Age (mean years)	54.3	54.4	0.44
Education (mean years)	14.5	14.0	0.08
Physical activity (mean score)	7.76	7.15	0.0005
Current cigarette smoking (%)	16.5	19.0	0.58
History of major depression (%)	19.3	26.5	0.13

P values were corrected for pair cluster using GEE regression.

MetS: Metabolic Syndrome

Table II

Mean levels of BDI score and subscores in twins with and without the metabolic syndrome (MetS).

Depressive Symptoms	Presence of MetS		*P* Value (Unadjusted)	*P* Value (Adjusted) *
	No	Yes		
BDI - total score	4.01	5.77	0.003	0.005
BDI - neurovegetative function	2.41	3.48	0.003	0.005
BDI - mood	0.75	1.07	0.038	0.048
BDI - negative affect	0.85	1.22	0.023	0.028

BDI = Beck Depression Inventory.

MetS: Metabolic Syndrome

* Adjusted for age, education, and current smoking. *P* values were corrected for pair cluster using GEE regression.

Table III

Mean levels of inflammatory markers in twins with and without the metabolic syndrome (MetS).

Inflammatory markers	Presence of MetS		% Difference	*P* Value (Unadjusted)	*P* Value (Adjusted)*
	No	Yes			
CRP (mg/L)†	1.62	3.07	89.5	< 0.0001	< 0.0001
IL-6 (pg/mL)	2.05	2.62	27.8	0.0003	0.0005
TNF-a (pg/mL)	1.45	1.58	9.0	0.096	0.063
sIL-6R (pg/mL)	28.6	29.9	4.5	0.398	0.438
sTNF-RII (pg/mL)	1.98	2.15	8.6	0.013	0.029

CRP = C reactive protein; IL-6 = interleukin-6; TNF-a = tumor necrosis factor alpha; sIL-6R = soluble IL-6 receptor; sTNF-RII = soluble TNF receptor

MetS: Metabolic Syndrome

* Adjusted for age, education and current smoking. *P* values were corrected for pair cluster using GEE regression.

† Data were missing for 2 twins with MetS and in 2 twins without MetS

Table IV

Correlations between inflammatory markers and depressive symptoms.

	CRP	IL-6	TNF-a	sIL-6R	sTNF-RII
BDI - total score	0.15*	0.19*	0.06	−0.002	0.11*
BDI - neurovegetative function	0.14*	0.17*	0.07	−0.01	0.12*
BDI - mood	0.11	0.19*	0.04	−0.01	0.10
BDI - negative affect	0.13*	0.16*	0.04	0.02	0.06

CRP = C reactive protein; IL-6 = interleukin-6; TNF-a = tumor necrosis factor alpha; sIL-6R = soluble IL-6 receptor; sTNF-RII = soluble TNF receptor; BDI = Beck Depression Inventory.

* $P < 0.05$ (corrected for pair cluster using GEE regression).

Table V

Association of metabolic syndrome (MetS) and inflammatory markers with depressive symptoms (BDI - total score and BDI subscales).

	Dependent Variable											
	BDI Total Score			BDI Neurovegetative Subscore			BDI Mood Subscore			BDI Affective-Cognitive Subscore		
	Beta	F	P	Beta	F	P	Beta	F	P	Beta	F	P
Unadjusted Model												
CRP	0.81	6.25	0.01	0.42	5.51	0.02	0.16	3.74	0.055	0.23	5.25	0.02
IL-6	1.85	11.7	0.0008	0.91	9.25	0.003	0.46	11.11	0.001	0.48	8.04	0.005
Combined Inflammation	2.68	12.55	0.0005	1.31	9.73	0.002	0.71	13.6	0.0003	0.68	8.22	0.005
Model 1: Initial Model												
Metabolic Syndrome	1.66	5.6	0.02	1.01	6.8	0.01	0.30	2.61	0.10	0.37	2.82	0.09
Model 2: Adjusting for CRP												
Metabolic Syndrome	1.50	4.07	0.04	0.95	5.42	0.02	0.25	1.70	0.19	0.30	1.67	0.20
CRP	0.31	0.91	0.34	0.13	0.50	0.48	0.06	0.55	0.46	0.12	1.46	0.23
Model 3: Adjusting for IL-6												
Metabolic Syndrome	1.39	3.71	0.056	0.89	4.96	0.03	0.20	1.14	0.29	0.32	1.97	0.16
IL-6	0.99	3.17	0.08	0.44	2.08	0.15	0.30	4.14	0.04	0.25	2.06	0.15
Model 4: Adjusting for Combined Inflammation												
Metabolic Syndrome	1.29	3.07	0.08	0.88	4.68	0.03	0.18	0.84	0.36	0.24	1.10	0.29
Combined Inflammation	1.55	3.87	0.051	0.63	2.09	0.15	0.51	6.24	0.01	0.43	3.05	0.08

The initial model, models 2 and 3 were adjusted for age, education and current smoking. *P* values were corrected for pair cluster using mixed regression models.

BDI: Beck Depression Inventory; CRP = C reactive protein; IL-6 = interleukin-6; MetS: Metabolic Syndrome

Combined inflammation was defined using both CRP and IL-6 levels, with high inflammation corresponding to the co-existence of both high levels of CRP (≥ median: 1.34 mg/L) and high levels of IL-6 (≥ median: 1.66 pg/mL).