Inflammatory Biomarkers in 70 Depressed Inpatients With and Without the Metabolic Syndrome

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Objective: Chronic subclinical inflammation may be associated with the metabolic syndrome as well as with depression. We examined the impact of the metabolic syndrome on concentrations of inflammatory biomarkers in major depression.

Method: Data for 70 inpatients with major depressive disorder (diagnosed according to *ICD-10* and *DSM-IV*), and with or without the metabolic syndrome, were assessed 4 to 5 weeks after admission to the clinic of the Department of Psychiatry, Charité-University Medicine, Berlin, between 2005 and 2007. The metabolic syndrome was defined according to the criteria of the International Diabetes Federation (2005). Immunologic biomarkers assessed included adiponectin, resistin, serum amyloid A (SAA), C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), soluble E-selectin, and CD40 ligand (CD40L). Severity of depression was measured with the 17-item Hamilton Depression Rating Scale.

Results: After regressional correction for confounding variables and covariates, a 2-factorial analysis of variance (metabolic syndrome × time) revealed that the metabolic syndrome's presence affected adiponectin ($F_{43,1} = 5.56$; $P < .05$) and IL-6 levels ($F_{25,1} = 6.80$; $P < .05$) significantly. There was also a trend for effects on fibrinogen levels ($F_{47,1} = 3.66$; $P = .06$).

Conclusions: This is the first study to evaluate the putative additive effect of the metabolic syndrome on a panel of 9 inflammatory biomarkers in depression. Our findings support an additive effect on some (adiponectin, IL-6, and trendwise for fibrinogen) markers. Patients with the metabolic syndrome and major depression are at higher risk for more frequent and more severe cardiovascular side effects than their counterparts without the metabolic syndrome.

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There is growing evidence that depression affects physical health. However, there are still open questions with regard to the mechanisms that may account for poor health outcomes associated with depression. Previous reports have speculated that depression may be linked to adverse health outcomes through an association with the metabolic syndrome.[1] In a recent review[2] comprising publications since 1966, Jakovljević and colleagues summarized that 24.6%–50.0% of bipolar patients and 12%–36% of the patients with recurrent depression have also been reported to have the metabolic syndrome.

Depression influences glucose metabolism and the risk for diabetes. These associations are believed to be maintained mainly through central adiposity.[3] Capuron et al[4] found a strong association between depressive symptoms and the metabolic syndrome, which they suggest is at least partly mediated by inflammation.

The Metabolic Syndrome

The constellation of metabolic disturbances, which are all risk factors for cardiovascular disease, was first described by Kylin[5] and thereafter elaborated on by Vague,[6] who drew attention to upper body adiposity in this context. Subsequently, Reaven[7] called attention to the relationship between insulin resistance, hyperglycemia, dyslipidemia, hypertension, and cardiovascular disease.

While the concept of the metabolic syndrome as such is being approved of, there is still some controversy about an internationally accepted and consistent definition. In sum, however, the metabolic syndrome is being considered a cluster of metabolic abnormalities, including disturbed glucose and insulin metabolism, hypertension, dyslipidemia, and centrally distributed obesity.[8]

The prevalence of the metabolic syndrome has previously been examined in association with different psychiatric diseases.[9,10] However, the relationship between major depression and the metabolic syndrome has so far been studied only in young (17–39 years of age) US-American adults[11] and in a few Finnish studies.[9,12-14]

Much evidence suggests that the metabolic syndrome can entail depressivity.[9,12] Conversely, depressive symptoms can promote the metabolic syndrome longitudinally, as well.[13–15]

The associations between psychopathology and the metabolic syndrome can be explained by different putative mechanisms: First, disadvantageous health behaviors such as smoking or nonadherence to pharmacotherapy could lead to metabolic consequences. Physical inactivity and dietary changes accompanying a depressive episode might also play a role, although this path of explanation has repeatedly only partly explained the observations. Second, psychosocial variables such as depressive mood entail alterations in the autonomic nervous system, such as elevated heart rate and reduced heart rate variability, hypothalamic-pituitary-adrenal-axis activity, levels of hemostatic and proinflammatory cytokines, and white blood cell count.[16] These have

also been recognized as important in the development of the metabolic syndrome.

Räikkönen et al[13] draw attention to a possible explanation stemming from a neurotransmitter approach. Depression and other negative emotions are associated with a blunted central serotonin release, which in turn has been associated with the metabolic syndrome.[17] Furthermore, it could also be that the psychosocial as well as metabolic factors share a common underlying factor.[18]

The Metabolic Syndrome and Inflammation

As has been hinted above, chronic subclinical inflammation is assumed to be part of the metabolic syndrome.[19,20] While inflammatory markers are not currently included in the diagnostic criteria for the metabolic syndrome, several studies add support to the concept that a proinflammatory state is one component of this syndrome.[21,22] Inflammatory markers that have been linked to the metabolic syndrome, and to being present in the visceral fat, include C-reactive protein (CRP), tumor necrosis factor-α, fibrinogen, interleukin-6, leptin, resistin, and adiponectin, among others.[23] Adipose tissue of obese individuals secretes increased amounts of these molecules compared to adipose tissue of lean individuals.[24] Even though the link between inflammation and the metabolic syndrome is not fully understood, one putative pathway linking inflammatory processes with the metabolic syndrome might be a stimulated CRP production via the liver, triggered by cytokines, which have been released from adipose tissue into the circulation. Weisberg et al[24] showed that macrophage infiltration into adipose tissue in obesity could be a source of inflammatory substances. Another possible explanation is that insulin resistance is causal and responsible for a higher production of cytokines. It has been shown that CRP concentrations are elevated predominantly in obese individuals who are also insulin resistant and that CRP levels fall in parallel with weight loss–associated improvements in insulin action.[25] Thus, they themselves might be partly responsible for the metabolic, hemodynamic, and hemostatic abnormalities that cluster with insulin resistance.

Depression and Activation of the Inflammatory System

There is now abundant evidence that major depression is accompanied by changes in the immune system,[26–29] especially in terms of an imbalance between proinflammatory and anti-inflammatory cytokines. A role for cytokines in depression was first proposed by Smith[30] and has since been extensively studied. On the one hand, depression may be the consequence of inflammation;[31] on the other hand, depression may cause inflammation through altered neuroendocrine function and central adiposity.[32] An important inspiration in this area of research arose from observations of patients being treated with proinflammatory cytokines, eg, in cancer and hepatitis C, together with animal studies of systematic administrations of lipopolysaccharide (LPS) that induces the expression of proinflammatory cytokines.[33] Patients experienced symptoms such as weakness, nausea, apathy, lethargy, loss of interest in their surroundings, loss of libido and appetite, and sleep disturbances, and they had difficulties concentrating. Mice displayed decreased motor activity, social withdrawal, reduced water and food intake, altered cognition, and increased slow-wave sleep. Taken together, these symptoms are referred to as "sickness behavior," which strikingly resembles the symptoms of major depression.

According to Smith's "macrophage theory of depression,"[30] the excessive secretion of macrophage monokines is proposed to be the cause of depression, as they can provoke the hormonal abnormalities linked with depression as well as disturb serotonin metabolism and cause the typical neurovegetative symptoms. Furthermore, this theory can account for several depression-associated facts, such as prevalence rates in different subpopulations, comorbidities, and the like. The author points out that macrophage activation also occurs in coronary heart disease, rheumatoid arthritis, and stroke, all of which are significantly associated with major depression.[30] In addition, the higher number of women affected by major depression could be due to estrogen's ability to activate macrophages. The extraordinarily low rate of depression in Japan is consistent with the suppressive effect of eicosapentaenoic acid (an omega-3 fatty acid), abundant in the Japanese diet, on macrophages.

More recent hypotheses on cytokines' putative role in major depression draw attention to the effect of cytokines on tryptophan metabolism, particularly the kynurenine pathway. This pathway is initiated by indoleamine 2,3-dioxygenase (IDO), which is evoked by proinflammatory cytokines, eg, when under stress, thus promoting the kynurenine pathway at the cost of the serotonin pathway.[34]

Furthermore, Vaccarino et al[35] collected evidence for a common genetic substrate linking depression and inflammation, suggesting that both share a common pathophysiologic mechanism.

Alterations in plasma cytokine levels have now been repeatedly found in patients suffering from affective disorders.[36,37] It has to be noted, however, that conflicting results have also been described.[38,39]

Current Study

Given the fact that both major depression and the metabolic syndrome appear to be associated with immunity related changes, and given the fact that depression and the metabolic syndrome appear to increase the probability of a mutual appearance, it is of great interest to us to examine putative additive effects on immunity of one condition on the other.

Thus, the aim of our current study was to examine the impact of the metabolic syndrome on concentrations of inflammatory biomarkers in patients with major depression at baseline and after amelioration of depressive symptomatology.

The following immunologic biomarkers were assessed: the adipocytokines adiponectin and resistin; the acute-phase proteins serum-amyloid A (SAA), C-reactive

protein (CRP), fibrinogen, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α); the adhesion molecule soluble E-selectin (sE-selectin); and the blood platelet activating CD40 ligand (CD40L).

Adiponectin is the most abundant adipose-derived plasma protein with anti-inflammatory qualities that has been observed to be decreased in major depression[40] as well as in obese subjects and in the metabolic syndrome.[41] Serum-amyloid A is an acute-phase protein that has been found to be elevated in remitted depressed women[42] and in patients with the metabolic syndrome.[43] The acute-phase protein CRP, also an unspecific marker of systemic inflammation, has been observed to be elevated in depression[44] and in the metabolic syndrome.[45] Interleukin-6 is produced by a variety of cell types such as monocytes, endothelial cells, lymphoblasts, and adipocites. Increased IL-6 levels in depression[46] as well as a positive correlation with obesity, insulin resistance, and hypertension have been described.[47] The proinflammatory cytokine TNF-α, produced in adipose tissue and macrophages, has been shown to mirror the clinical course of depression[36] and to be overexpressed in the adipose tissue of obese subjects.[48] Resistin, expressed in fat cells, regulates glucose metabolism and promotes activation of endothelial cells. Elevated levels have been shown in obesity.[49] The only study that assessed resistin in association with severity of depression in a middle-aged and older Chinese population did not find increased levels.[50] The adhesion molecule sE-selectin is elevated in depression[51] and has been observed to be higher in Aboriginal subjects with as opposed to without the metabolic syndrome.[52] The hepatically synthesized acute-phase reactant fibrinogen has been discovered to be increased in depression[46] and to be associated with the metabolic syndrome.[53] The CD40 ligand, from the TNF family, plays a role in the activation of blood platelets and has been described to be higher in depressed patients when compared to healthy controls.[40] There are also suggestions for an up-regulation of CD40L in the metabolic syndrome.[54]

METHOD

Subjects and Study Design

Seventy-one patients who were referred to the Department of Psychiatry, Charité-University Medicine, Berlin, between 2005 and 2007 were approached to participate in the "Endophänotypisierung affektiver Erkrankungen" ("endophenotyping of affective disorders") study, part of which is presented here. The study was approved by the ethics committee of Charité and all patients gave their written informed consent to participate. All patients suffered from a depressive episode when admitted to the hospital; the individual diagnosis varied within the range of the affective disorders spectrum (F31, F32, and F33 for *ICD-10* diagnoses and 296.XX for *DSM-IV* diagnoses). Patients with an acute respiratory infection up to 2 weeks before assessment, or during the study, were excluded.

Patients with a history of drug or alcohol abuse within 1 year prior to admission were also excluded from the study, as were patients who were taking anti-inflammatory medication. Furthermore, schizophrenia or schizoaffective patients were excluded. Exclusion criteria, however, included active medical illness that could etiologically be related to the ongoing depression (eg, untreated hypothyroidism or uncontrolled diabetes), as well as immune and autoimmune diseases.

During the course of the study, 1 patient had to be excluded from further analysis due to the development of a common cold.

Data were assessed at 2 time points: at T1, within a few days after referral to the clinic, and at T2, which was 4 to 5 weeks after the beginning of inpatient treatment.

Thus, measures of depression as well as inflammatory biomarkers were gathered at 2 time points. In addition to that, metabolic syndrome and sociodemographic variables were collected at T1. Clinical and laboratory data were anonymous, and all ratings were performed by trained psychiatrists and clinical psychologists who were blind to the immunologic results.

Major Depression

The diagnosis using *DSM-IV* and *ICD-10* criteria was verified using the German version of the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) (Strukturiertes Klinisches Interview für *DSM-IV*, Achse I [SKID-I]).[55] Severity of depression was quantified with the 17-item Hamilton Depression Rating Scale (HDRS).[56] In addition, we also assessed the lifetime number of depressive episodes, duration of the current episode, and past suicide attempts to further characterize the patients' depressive disorders.

Sociodemographic and clinical data assessed included factors and conditions known to be associated with depressed mood or with inflammatory markers in the literature, such as age, gender, smoking status, alcohol use, body mass index (BMI = kg/m^2), and medication status.

Metabolic syndrome was assessed at admission according to the criteria of the International Diabetes Federation (IDF),[57] which state the following: for a person to be defined as having the metabolic syndrome, they must have central obesity defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women. If the BMI of the respective person is above 30, central obesity can be assumed and waist circumference does not need to be measured. On top of that, any 2 of the following 4 factors should be met: (1) raised triglycerides, ie, ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality; (2) reduced high-density lipoprotein cholesterol, ie, < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality; (3) raised blood pressure, ie, systolic blood pressure ≥ 130 mm/Hg or diastolic blood pressure ≥ 85 mm/Hg, or specific treatment of previously diagnosed hypertension; and (4) raised fasting plasma glucose, ie, ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

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The study followed a naturalistic design, ie, all patients were treated according to their psychiatrist's choice with different kinds of antidepressant drugs, psychotherapy, and adjunctive methods, with the dosage adjusted according to clinical judgment and plasma levels.

Immunologic Biomarkers

Blood was drawn in the early morning hours through antecubital venipuncture following an overnight fast. The blood was then centrifuged at 3000g for 10 minutes, immediately divided into aliquots, and frozen at −70°C until analysis.

Inflammatory parameters were analyzed using standard enzyme-linked immunoabsorbent assay for adiponectin, IL-6, TNF-α, resistin, sE-selectin, and CD40L (all R&D Systems, Wiesbaden-Nordenstadt, Germany). Serum amyloid A, CRP, and fibrinogen were analyzed as described before.[58]

Due to technical difficulties in the laboratory assessing the inflammatory biomarkers, levels of IL-6 and CD40L were assessed in only half of the subjects.

Statistical Analysis

The goal of this study was to examine the impact of the metabolic syndrome on levels of inflammatory biomarkers in patients with major depression at 2 measurement points. Differences in characteristics between patients with and without the metabolic syndrome were compared with independent-samples *t* tests for continuous variables and with χ^2 tests for dichotomous variables. The influence of the thus-yielded confounding variables was determined with forced-entry multiple regression analyses in a first step. These analyses also yielded the residuals of the dependent variables freed from the influence of the covariates. To calculate their impact on the inflammatory biomarkers, those residuals were entered into a 2-factorial analysis of variance, with the first factor being the metabolic syndrome purged from the influence of the confounding variables and the second factor being the time point of data acquisition (mirroring the amelioration of depressive symptoms).

Paired-samples *t* tests should detect whether patients' severity of depression as quantified via the HDRS differed across the 2 time points of assessment across both groups as well as for each group separately. Independent-samples *t* tests were carried out to look for changes in the respective scale scores as well as response to treatment (quantified as improvement between T1 and T2 on the depression scale) between the 2 patient groups.

Hamilton Depression Rating Scale scores were also added as covariates into the regression analyses to assess their influence on the concentrations of the inflammatory biomarkers.

RESULTS

After applying the IDF definition criteria, we identified 17 patients (24%) as having the metabolic syndrome and 53 patients (76%) without it.

Table 1. Demographic and Clinical Variables of 70 Patients With Major Depressive Disorder With and Without Metabolic Syndrome

Variable	With Metabolic Syndrome (n = 17)	Without Metabolic Syndrome (n = 53)
Sex		
Male, n	6	18
Female, n	11	35
Age, mean (SD), y[a]	55.56 (13.45)	45.38 (13.10)
No. of depressive episodes, mean (SD)	6.19 (7.96)	4.68 (5.73)
Duration of illness, mean (SD), wk[a]	13.00 (15.84)	42.80 (71.16)
No. of suicide attempts, mean (SD)[a]	0.20 (0.41)	0.56 (0.95)
HDRS score at time point 1, mean (SD)	19.92 (6.34)	20.79 (5.34)
HDRS score at time point 2, mean (SD)	11.50 (5.45)	12.56 (4.67)

[a]Indicates significance at $P < .05$.
Abbreviation: HDRS = 17-item Hamilton Depression Rating Scale.

Sociodemographic and Depression Variables

As shown in Table 1, independent-samples *t* tests revealed that patients with the metabolic symptom were significantly older than the patient group without the metabolic syndrome ($t_{67} = 2.71$; $P < .05$). Patients with the metabolic syndrome were furthermore experiencing significantly shorter durations of the current episode ($t_{63} = -2.79$; $P < .05$) and had significantly less suicide attempts ($t_{54} = -2.10$; $P < .05$) in their history. The range of the duration of the current episode was 2 to 47 weeks in the patient group with the metabolic syndrome, and 2 to 300 weeks in the group without it. The latter group comprised all patients of our overall sample with chronic depression (ie, duration of illness < 2 years; n = 8). The 2 patient groups did not differ in the amount of episodes they had experienced overall ($t_{67} = .84$; $P = .40$).

The male/female ratio was approximately 1:2 in both groups. Nevertheless, we decided to add sex as a covariate into the subsequent analysis as there are reports in the literature that women and men have different concentrations of cytokines.[59]

Thus, sex, duration of the current episode, suicide attempts, and age were entered into a regression model to assess their effect on the respective inflammatory biomarkers.

Both patient groups taken together improved significantly in their psychopathology (as assessed with the HDRS) from inclusion in the study until the second time point of data assessment as revealed by the paired-samples *t* tests ($t_{50} = 8.53$, $P < .001$). Looked at separately, the patient group with the metabolic syndrome ($t_{11} = 3.64$, $P < .05$) as well as the patients without the metabolic syndrome ($t_{38} = 7.67$, $P < .001$) were significantly less depressed after 4 to 5 weeks of treatment. Independent-samples *t* tests showed that patients with the metabolic syndrome were neither more nor less severely depressed than patients without the metabolic syndrome at T1 ($t_{58} = -50$, $P = .62$) or at T2 ($t_{53} = -0.703$, $P = .49$). Paralleling this are the results for the response to treatment. Both patient groups did not differ from each other in the improvement of their HDRS scores ($t_{50} = -3.77$, $P = .13$) Adding

Table 2. Inflammatory Biomarkers at Time Point 1 (T1) and Time Point 2 (T2) in 70 Patients With Major Depressive Disorder With and Without Metabolic Syndrome[a]

	With Metabolic Syndrome (n = 17)		Without Metabolic Syndrome (n = 53)		All Patients (N = 70)	
Biomarker	T1	T2	T1	T2	T1	T2
Fibrinogen, g/L	3.16 (1.10)	3.18 (0.86)	2.69 (0.67)	3.04 (0.75)[b]	2.81 (0.82)	3.08 (0.78)[b]
Serum amyloid A, mg/L	4.39 (2.78)	4.74 (3.57)	4.79 (4.31)	6.41 (6.70)	4.69 (3.96)	5.99 (6.08)
C-reactive protein, mg/L	2.58 (2.68)	2.16 (2.22)	1.52 (2.21)	2.07 (2.35)	1.77 (2.35)	2.09 (2.30)
Interleukin-6, pg/mL	1.60 (0.46)	2.31 (0.50)	1.32 (0.90)	1.41 (0.69)	1.36 (0.84)	1.55 (0.73)
Adiponectin, ng/mL	7,203.58 (4,119.21)	4,536.66 (2,039.57)[b]	10,446.36 (6,278.19)	10,342.39 (8,071.80)	96,661.82 (5,964.71)	8,937.78 (7,508.02)
Tumor necrosis factor-α, pg/mL	1.60 (1.31)	1.37 (1.37)	1.61 (3.19)	1.53 (1.85)	1.61 (2.81)	1.49 (1.72)
Resistin, ng/mL	12.09 (5.44)	11.82 (5.25)	11.41 (4.01)	11.26 (3.54)	11.57 (4.36)	11.39 (3.98)
Soluble E-selectin, ng/mL	28.30 (10.94)	26.33 (10.63)	26.19 (13.12)	27.09 (13.47)	26.70 (12.58)	26.90 (12.76)
CD40 ligand, ng/mL	7.63 (2.50)	9.70 (6.34)	8.51 (3.78)	8.75 (4.90)	8.22 (3.40)	9.05 (5.34)

[a]Data are expressed as mean (SD).
[b]Indicates significance at $P < .05$ between T1 and T2 within the respective groups (metabolic syndrome vs no metabolic syndrome vs all patients).

severity of depression as quantified by the HDRS scale to the regression analyses did not yield any significant effects on inflammatory biomarker concentration with the one exception of CD40L at T2 ($t_{15} = -2.24$, $P < .05$).

Impact of Covariates and Confounding Variables on Inflammatory Biomarkers Across Groups

Multiple regression analyses revealed that age, past suicide attempts, duration of current episode, and sex did all not contribute significantly to SAA, fibrinogen, CRP, and sE-selectin at T1 as well as at T2.

Sex contributed significantly to adiponectin levels at T1 ($t_{45} = 2.23$, $P < .05$). Age and suicide attempts in the past made significant contributions to adiponectin levels at T2 ($t_{45} = 2.16$; $P < .05$ and $t_{45} = 2.11$; $P < .05$ for age and suicide attempts, respectively). Age contributed significantly to IL-6 levels at T2 ($t_{23} = 2.82$; $P < .05$), but none of the putative confounding variables contributed significantly to IL-6 values at T1 or T2. Past suicide attempts contributed significantly to TNF-α levels at T1 ($t_{46} = 3.22$; $P < .05$) as well as at T2 ($t_{46} = 2.94$; $P < .05$). Sex contributed significantly to resistin concentrations at T2 ($t_{45} = 2.32$, $P < .05$), but none of the putative confounding variables contributed significantly to resistin values at T1 or T2. CD40L levels were affected significantly only by HDRS scores at T2 ($t_{15} = -2.24$, $P < .05$).

Metabolic Syndrome and Inflammatory Biomarkers

Table 2 shows the comparison of the levels of inflammatory biomarkers. The subsequent 2-factorial analyses of variance yielded a significant effect of the metabolic syndrome on adiponectin levels ($F_{43,1} = 5.56$; $P < .05$, $\eta^2 = .11$). The factor time did not yield any significant influences on adiponectin; neither did the interaction of the 2 factors ($F_{54,1} = 0.55$; $P = .461$; $\eta^2 = .01$ and $F_{54,1} = 1.79$; $P = .19$; $\eta^2 = .03$, respectively) (Table 3).

The metabolic syndrome did not affect SAA levels ($F_{45,1} = 2.56$; $P = .12$; $\eta^2 = .05$). Neither did the factor time ($F_{45,1} = 0.02$; $P = .89$; $\eta^2 = .00$) or the interaction of metabolic syndrome and time ($F_{45,1} = 0.50$; $P = .48$; $\eta^2 = .01$).

There was a trend for the influence of the metabolic syndrome on fibrinogen levels ($F_{47,1} = 3.66$; $P = .06$; $\eta^2 = .08$), but there was no effect of time ($F_{47,1} = 1.56$; $P = .22$; $\eta^2 = .03$). The interaction, however, proved to be significant again ($F_{47,1} = 4.13$; $P < .05$; $\eta^2 = .08$).

The factor metabolic syndrome did not influence CRP levels significantly ($F_{46,1} = 1.98$; $P = .17$; $\eta^2 = .04$); neither did the factor time ($F_{46,1} = 1.45$; $P = .23$; $\eta^2 = .03$) or the interaction ($F_{46,1} = 1.44$; $P = .24$; $\eta^2 = .03$).

IL-6 levels were significantly influenced by the absence or presence of the metabolic syndrome ($F_{25,1} = 6.80$; $P < .05$; $\eta^2 = .21$). Time, however, did not play a significant role ($F_{25,1} = 0.07$; $P = .80$; $\eta^2 = .00$). The same applies to the interaction ($F_{25,1} = 0.37$; $P = .55$; $\eta^2 = .02$).

TNF-α levels were not influenced on a significant level by the metabolic syndrome ($F_{46,1} = 0.33$; $P = .57$; $\eta^2 = .01$), the factor time ($F_{46,1} = 0.24$; $P = .62$; $\eta^2 = .01$), or their interaction ($F_{46,1} = 0.06$; $P = .81$; $\eta^2 = .00$).

The results for resistin were similar; there was no significant effect of the metabolic syndrome ($F_{43,1} = 1.46$; $P = .23$; $\eta^2 = .03$), time ($F_{43,1} = 0.00$; $P = .98$; $\eta^2 = .00$), or their interaction ($F_{43,1} = 0.43$; $P = .51$; $\eta^2 = .01$).

In almost the same manner, no significant effect of metabolic syndrome ($F_{43,1} = 0.09$; $P = .77$; $\eta^2 = .00$), time ($F_{43,1} = 0.23$; $P = .64$; $\eta^2 = .01$), or their interaction ($F_{43,1} = 0.30$; $P = .59$; $\eta^2 = .01$) was found for sE-selectin.

Likewise, CD40L levels were not significantly affected by the metabolic syndrome ($F_{16,1} = 0.01$; $P = .93$; $\eta^2 = .00$), by the factor time ($F_{16,1} = 0.09$; $P = .77$; $\eta^2 = .01$), or by their interaction ($F_{16,1} = 1.62$; $P = .22$; $\eta^2 = .09$).

DISCUSSION

Past research has indicated that major depression as well as the metabolic syndrome can lead to an increase of proinflammatory cytokines. This is the first study to evaluate the putative additive effect of the metabolic syndrome in depression on inflammatory biomarkers. We presented a comprehensive panel of 9 cytokines measured in depressed inpatients with or without the metabolic syndrome.

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Table 3. Inflammatory Biomarker Profiles in 70 Patients With Major Depressive Disorder With and Without Metabolic Syndrome at Time Point 1[a]

Biomarker	With Metabolic Syndrome (n = 17)	Without Metabolic Syndrome (n = 53)	*P* Value
Fibrinogen, g/L	3.16 (1.10)	2.69 (0.67)	.062
Serum amyloid A, mg/L	4.39 (2.78)	4.79 (4.31)	NS
C-reactive protein, mg/L	2.58 (2.68)	1.52 (2.21)	NS
Interleukin-6, pg/mL	1.60 (0.46)	1.32 (0.90)	< .05
Adiponectin, ng/mL	7,203.58 (4,119.21)	10,446.36 (6,278.19)	< .05
Tumor necrosis factor-α, pg/mL	1.60 (1.31)	1.61 (3.19)	NS
Resistin, ng/mL	12.08 (5.44)	11.41 (4.01)	NS
Soluble E-selectin, ng/mL	28.30 (10.94)	26.19 (13.12)	NS
CD40 ligand, ng/mL	7.63 (2.50)	8.51 (3.78)	NS

[a]Data are expressed as mean (SD).
Abbreviation: NS = not significant.

About one-quarter of our depressed patients had a metabolic syndrome. This parallels the findings of a recent review.[2]

After freeing the data from all confounding variables and covariates that were assessed, the metabolic syndrome had an additive effect on some but not all proinflammatory biomarkers in our patient group.

Adiponectin levels were significantly decreased in the patient group with the metabolic syndrome and major depression. This expands and complements previous reports that have shown decreased levels of this most abundant adipose-derived plasma protein in patients with the metabolic syndrome[41,54] and in major depression as depicted by a study showing decreased adiponectin levels in first-episode drug-naïve depressed patients,[40] and in previously depressed medicated remitted patients.[60] We also found significantly increased IL-6 values in the patients group with the metabolic syndrome. Several studies yield support for this finding. IL-6 has been examined in an array of studies under diverse experimental conditions, the majority of which have shown an increase in the blood levels of this cytokine in major depression.[46,61,62] The presence of the metabolic syndrome has also been observed to raise IL-6 levels.[41] Reilly et al[63] report an increase of IL-6 levels of 56% in patients with the metabolic syndrome that furthermore were independently associated with coronary artery calcification. We also observed a trend for increased fibrinogen levels in the patient group with the metabolic syndrome. Elevated levels of this acute-phase reactant have been found previously in major depression[44,46] as well as in patients with the metabolic syndrome.[53]

Hence, taken together, for adiponectin and IL-6, and trendwise for fibrinogen, we could expand the previous findings in the sense of an additive effect of the metabolic syndrome on the respective biomarker's levels.

The metabolic syndrome's consequences can be severe. As mentioned above, the metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease. In a study investigating the age- and sex-specific prevalence of the metabolic syndrome and its association with all-cause and cardiovascular mortality in nondiabetic European men and women, Hu et al[64] found that nondiabetic persons with the metabolic syndrome had an increased risk of death from all causes including cardiovascular disease. The overall hazard ratios for all-cause and cardiovascular mortality in people with the metabolic syndrome as compared to those without it were 1.44 and 2.26 in men and 1.38 and 2.78 in women after the adjustment for age, blood cholesterol, concentrations, and smoking. In a cohort of women with suspected coronary artery disease, Vaccarino et al[65] observed that those with depression were 20% more likely to have the metabolic syndrome compared to those women who were not depressed. Cox proportional hazards modeling revealed that 20% of the cardiovascular risk associated with depression was explained by the metabolic syndrome in their study population.

Thus, patients with the metabolic syndrome in addition to major depression are at high risk to suffer from more frequent and more severe cardiovascular side effects than their counterparts without the metabolic syndrome. This finding is clinically highly significant since certain antidepressant treatment strategies (eg, atypical antipsychotics and mood stabilizers for augmentation) have the potential to cause or initiate or worsen metabolic symptoms. Thus treating depression should also aim at preventing, ameliorating, or cotreating the metabolic syndrome with regard to future cardiovascular complications for the respective patients.

Interestingly, not all biomarkers were affected by the presence of the metabolic syndrome. For the remaining markers, no additive effect of the metabolic syndrome on top of major depression was detected despite previous reports on associations between CRP,[45] SAA,[42] sE-selectin,[52] and CD40L levels[54] in the metabolic syndrome, and for TNF-α[48] and resistin[49] in obesity. However, it has to be noted that not all inflammatory markers presented here have been studied extensively so far in relation to depression or the metabolic syndrome. Some, such as SAA, CD40L, or resistin, have been so far assessed only in selected subgroups or small samples. Findings will have to be replicated for firmer interpretation.

One possible explanation for our results could be that even though not all patients met the definition criteria for the metabolic syndrome as such, 16 patients without the actual syndrome had at least 1 symptom out of the metabolic cluster, and another 8 patients 2 symptoms in addition to their depression, which might account for or at least contribute to their respective cytokine profile. It has been shown already that central fat alone can account for substantially increased levels of CRP, IL-6, TNF-α, amyloid A, and white blood cell count.[44] More research in this area is required to illuminate systematically the impact of hypertension, glucose and insulin metabolism, dyslipidemia, and centrally distributed fat in patients with major depression on proinflammatory and anti-inflammatory cytokines.

We also found that the patient group with the metabolic syndrome experienced significantly shorter durations of their current episode and had significantly less suicide attempts. Steiner et al[66] were the first ones to address the question of neuroimmunological alterations in the context of suicide. They found an increased microglial density in post mortem brain tissue of patients who had committed suicide independent of diagnosis (schizophrenia or depression) suggesting an enhanced inflammatory activation in these patients prior to death. We, by contrast, observed that the group with higher levels of inflammatory biomarkers (the group with the metabolic syndrome) had significantly less suicide attempts in their history. A direct comparison between our study and the one by Steiner and colleagues[66] is difficult, however. While Steiner et al investigated the actual suicide victims, we collected data from "survivors." We are not in the position to tell whether there are more or less suicide completers with the metabolic syndrome or in patients with high levels of proinflammatory cytokines. Regarding the results of Steiner et al, there is also the possibility that microglial activation was present only perisuicidally, ie, acutely prior to or during suicide, and is not correlated with chronic or prolonged suicidal ideations.

It would be interesting to know whether microglial activation correlated with measures of suicidality prior to commitment. Furthermore, Steiner et al[66] collected tissue from the brain, whereas our blood samples were drawn from the periphery, which makes comparisons complicated.

Moreover, there are factors other than immune parameters that reportedly correlate with suicidality, such as cholesterol levels.[67,68] But even though there are some studies linking low total cholesterol (and high cholesterol being a key symptom of the metabolic syndrome) to increased suicidal risk, our findings are most probably only an artifact due to the small sample size. Bigger samples are necessary to either support or refute our observations.

The patients in our study with the metabolic syndrome were also significantly older than the group without the metabolic syndrome. This finding has been reported before in several population-based studies that found an increase in the prevalence of the metabolic syndrome with age.[69]

We did not find an impact of severity of depression as measured by the HDRS on levels of inflammation. Even though our patients were significantly more depressed at the beginning of the study then after 4–5 weeks, the time point of assessment of severity of depression did not have an influence on inflammatory levels. However, when severity of depression was characterized as suicide attempts in the history an influence was depicted on adiponectin and TNF-α levels. Because depression itself is a proinflammatory state, there could also be a ceiling effect for some of the inflammatory biomarkers, which was not further increased by the metabolic syndrome.

It could also be argued that the naturalistic clinical conditions of our study could have influenced the blood levels of the markers assessed.[62] Nearly all patients were admitted premedicated and all patients received psychopharmacological treatment from admission onwards. Studies conducted eg, by Basterzi et al,[70] Szuster-Ciesielska et al,[71] and O'Brien et al[72] showed that antidepressant treatment has the potential to suppress proinflammatory cytokines at least in vitro in healthy volunteers, or only in patients that responded to selective serotonin reuptake inhibitor treatment, respectively. However, neither did we explicitly fail to replicate previously published findings of anti-inflammatory properties of antidepressants, nor does our study add support to it. Due to the fact that our study design did not include a drug free control-group or time-period we are actually not in the position to deduce statements considering putative anti-inflammatory actions based on our data. All our patients were treated at all times of data assessment according to clinical practice, which means that any immunoregulatory effects of the medications given was evenly spread across both groups (metabolic syndrome vs no metabolic syndrome). Despite that fact, however, we still observed increased levels of proinflammatory cytokines in the group with the metabolic syndrome as compared to the nonmetabolic one. So, even though the antidepressants administered during the course of our study could have lowered the cytokine's levels hypothetically, this did not happen evenly across both study groups. Possibly the magnitude of the putative immunosuppressive properties of the antidepressants administered was not of the magnitude to reduce all increased cytokine levels evoked by the metabolic syndrome as opposed to depression alone. Different production sites or underlying pathways, at the end all leading to increased cytokine production, could be one reason for that. Whereas visceral fat is very likely to be contributing to a much higher extent to the increase in adiponectin, and IL-6 in the metabolic group, the nonmetabolic group is lacking this additional source of inflammatory biomarker generation or is not affected as much as the metabolic group. So, while hypothetically antidepressants might alter cytokine levels via their action on monoamine pathways, the visceral fat pathways might remain unaltered. Alternatively, it might be the case that the metabolic patients' immuno-activity is altered to such an extent that the putative immuno-suppressive actions of antidepressants do not suffice to counterbalance them.

A follow-up study with control groups (unmedicated vs medicated metabolic syndrome and unmedicated vs medicated patients without the metabolic syndrome) would be necessary to elucidate the above-described speculations further. A last note has also to be made on the fact that the finding of immuno-supressive properties of antidepressants has not been replicated throughout[73] or only in subgroups or only in a selection of the respective cytokines assessed.[36,74,75]

As far as underlying mechanisms have been concerned, 2 possible pathways linking depression to inflammation via weight accumulation have been proposed by Miller et al.[76] They examined the interrelationships between depression, adiposity, and inflammatory molecules. Structural equation modeling yielded the possibility of depression promoting weight accumulation, yielding an inflammatory response,

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which in turn can entail either an expanded adipose tissue release of IL-6 or a leptin-induced up-regulation of IL-6 release by white blood cells. Interestingly, the study did not gather any support for a sickness behavioral model in which the inflammatory molecules arising from expanded adipose tissue would provoke depressive symptoms. This finding together with our results and the aforementioned studies underlines the importance of an adequate diagnosis and treatment of depressive disorders, since they do appear to have the potential to induce weight gain followed by inflammatory modifications and that these modifications put the respective patients in great danger for cardiovascular diseases, which are known to be the leading cause of mortality.

Strengths of our study include the comprehensive assessment and analysis of a number of potential confounding variables, a standardized measurement of inflammatory biomarkers and after fasting for 12 hours, and a naturalistic design allowing for a realistic assessment of potential risks of the metabolic syndrome in depressed patients.

But of course, our study has some limitations, too. First causal inferences are limited due to the cross-sectional design. Second, even though we took great care to take many confounding factors and covariables into account, confounding variables such as physical activity, dietary intake or deleterious health behaviors were not assessed and could have thus constituted further influences on the present data.

We did not assess the levels of physical activity of our patients; physical activity has previously been shown to be able to have an impact on proinflammatory cytokines.[77] Physically active individuals with the metabolic syndrome were shown to have impressively reduced levels of CRP, white blood cell count, SAA, TNF-α, IL-6, and also fibrinogen.[77] Due to the severity of illness, our patients were generally exhibiting a tendency to lethargy, but leisure-time physical activity should be assessed in the future in order to rule out putative confounding effects in even severely depressed patients.

Similarly, dietary intake has been reported to potentially exhibit an influence on markers of inflammation.[78] Consumption of high-fat meals has been shown to lead to an increase in IL-6 and, transiently, of TNF-α levels in obese men.[79] However, we tried to take care of such influences via an overnight fast in all patients.

Moreover, due to the fact that IL-6 and CD40L levels were assessed in only half of the study population, the findings considering these 2 cytokines have to be interpreted with caution. Even though the metabolic/nonmetabolic ratios were the same as in the entire sample, the number of subjects was very limited.

In conclusion, taking into account the aforementioned limitations, our study demonstrated that the metabolic syndrome does have an effect on a number of inflammatory markers in severely depressed patients and that further studies should aim at investigating systematically the metabolic syndrome's single components in relation to immune parameters.

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