Serum Levels of Interleukin-6 and Interleukin-10 in Relation to Depression Scores in Patients with Cardiovascular Risk Factors

Thomas Meyer a, Beate Stanske b, Michael M. Kochen a, Andreas Cordes a, Iraz Yüksel a, Rolf Wachter a, Claus Lüers c, Martin Scherer d, Lutz Binder a, Burkert Pieske e & Christoph Herrmann-Lingen a

a University of Göttingen
b University of Düsseldorf
c University of Marburg
d University of Hamburg
e Medical University of Graz

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Serum Levels of Interleukin-6 and Interleukin-10 in Relation to Depression Scores in Patients with Cardiovascular Risk Factors

Thomas Meyer
University of Göttingen

Beate Stanske
University of Düsseldorf

Michael M. Kochen, Andreas Cordes, Iraz Yüksel, and Rolf Wachter
University of Göttingen

Claus Lüers
University of Marburg

Martin Scherer
University of Hamburg

Lutz Binder
University of Göttingen

Burkert Pieske
Medical University of Graz

Christoph Herrmann-Lingen
University of Göttingen

It is currently unknown whether elevated cytokine levels in depression are confined to any specific subgroup of depressive patients. In this study, medical out-patients presenting with cardiovascular risk factors (N = 356) were assessed for both cognitive–affective and physical symptoms of depression using the Hospital Anxiety and Depression Scale (HADS) and the Maastricht questionnaire (MQ), respectively. In study participants assigned to the highest (≥21) and lowest (≤5) quartile for the MQ score, serum levels of cytokines were measured.

We found highly significant associations between cognitive–affective symptoms of depression and elevated serum levels of interleukin-6 (IL-6; \( \rho = .231; p = .002 \)) and interleukin-10 (IL-10; \( \rho = .370; p < .001 \)), respectively. In multiple regression models elevated IL-10 serum concentration was independently related to cognitive–affective symptoms of depression (\( \rho = .165; p = .002 \)). When all cytokines were included in one model, elevated IL-10 serum concentrations remained a significant predictor for depressive mood (\( \rho = .157; p = .009 \)). In patients with cardiovascular risk factors and extreme scores for vital exhaustion, elevated serum IL-6 and even more IL-10 concentrations are linked to the presence of depressive mood. Future
Major depression, a common mental disorder, manifests with cognitive–affective symptoms such as sadness, feelings of worthlessness and guilt, as well as physical symptoms including exhaustion, loss of energy and others. A growing body of evidence points to the crucial role of cytokines and inflammatory responses in the pathogenesis of depression. Cross-sectional studies have reported that patients with depressive symptoms exhibit higher levels of circulating inflammatory markers, including interleukin-6 (IL-6), C-reactive protein and fibrinogen and that circulating IL-6 levels are a strong independent marker for increased mortality in patients with coronary artery disease. Major depression was reported to be accompanied by systemic immune activation, an acute phase response with increased plasma levels of acute phase proteins, and increased production of IL-6 by peripheral blood mononuclear cells.

Numerous studies have reported that depression is a risk factor for incident coronary artery disease and subclinical aortic and carotid atherosclerosis, whereas other studies did not find evidence for a correlation between depression and coronary-artery calcification. Several investigations have advanced the hypothesis that depressive symptoms accelerate the progression of atherosclerosis by fostering latent or chronic inflammatory processes. Pizzi and colleagues have found that in patients free of coronary heart disease (CHD), but with arteriosclerotic risk factor, depressive subjects were more likely to have higher C-reactive protein and IL-6 levels as compared with non-depressed individuals.

Epidemiological studies have suggested that also vital exhaustion or the presence of physical symptoms of depression is an independent risk factor for arteriosclerotic diseases including the occurrence of myocardial infarction and first stroke. Elevated plasma levels of pro-inflammatory cytokines in vitally exhausted patients have been proposed as a possible trigger for cardiovascular disease. In particular, IL-6 was shown to be associated with the diagnosis of myocardial infarction and coronary heart disease (CHD) in vitally exhausted patients.

However, the association between depression and interleukin-10 (IL-10) serum concentrations is less clear. Parissis et al. have demonstrated that elevated plasma levels of this anti-inflammatory cytokine predict adverse clinical outcome in chronic heart failure patients with depressive symptoms. Dowlati and colleagues presented data from a meta-analysis of six studies including a total of 171 depressed and 200 non-depressed individuals suggesting that IL-10 levels were not elevated in patients with major depression. Recently, we have reported that in primary care patients with cardiovascular risk factors IL-10 was independently related to vital exhaustion. In line, gene expression profiling conducted on post-mortem brain tissue samples from the prefrontal cortex has revealed that the human IL-10 gene is up-regulated in depressed patients.

The observation that cognitive–affective and physical symptoms of depression are both associated with athero-sclerotic diseases suggests a common pathophysiological link. In the present secondary analysis of our previous investigation we therefore focused on the research question whether the observed association between vital exhaustion and cytokines was only explained by physical symptoms of depression mainly constituting the Maastricht questionnaire or if there was also an association of cytokines with cognitive–affective symptoms of depression.

**METHODS**

**Participants and Procedure**

The study presented is part of the MedViP trial, an acronym which stands for “Medical care in general practice” (German: “Medizinische Versorgung in der Praxis”), that primarily aimed at improving medical treatment by primary care physicians. A total of 2,273 primary care patients from 58 medical practices in the Göttingen area were invited by their family physicians to participate in the study, if one or more known cardiovascular risk factors were identified. Patients over 18 years of age were included if they: (1) had a diagnosis of hypertension (blood pressure >140/90 mmHg) or were currently taking antihypertensive medication; (2) had a diagnosis of diabetes (glycated hemoglobin HbA1c >7%) or were currently engaged in anti-hyperglycemic therapy; (3) had a diagnosis of hyperlipoproteinemia (elevated LDL >130 mg/dl or total serum cholesterol >220 mg/dl); (4) were smokers; and/or (5) had a family history of chronic heart failure. Exclusion criteria were manifest congestive heart failure, angiographically determined ischemic or non-ischemic cardiomyopathy, severe cognitive impairment or other severe mental diseases (eg, psychosis, substance and alcohol abuse), and insufficient knowledge of the German language.

From all patients who agreed to participate in the study, written informed consent was obtained. The first 356 consecutive patients from this sample were considered for the current study. All study participants were interviewed and clinically examined by trained cardiologists at the University hospital. For each patient, body mass index (BMI) was calculated as the individual’s body weight in kilograms divided
by the square of height in meters. After enrollment, serum samples were obtained and stored in aliquots at −70°C until measurement. Participants were requested to complete, beside others, the German version of the Maastricht questionnaire (MQ) and the Hospital Anxiety and Depression Scale (HADS). Additionally, echocardiography was performed including measurements of left-ventricular ejection fraction (LVEF) and end-diastolic diameter (LVEDD). The previously published study protocol was approved by the local Institutional Ethics Review Board at the University of Göttingen.

Psychometric Tests

Vital exhaustion was assessed by means of the Maastricht questionnaire. This validated and well-established instrument, commonly used for the measurement of vital exhaustion, has been shown to predict outcome in CHD patients. The questionnaire consists of 21 items and each item is rated on a scale from 0 to 2. It mainly covers physical symptoms of depression such as fatigue, weakness, sleeping and concentration problems, loss of energy and libido but also cognitive–affective symptoms such as irritability and suicidal ideation. Depressive mood was measured by means of the Hospital Anxiety and Depression Scale (HADS). This widely used instrument was originally developed to assess self-reported anxiety and depression in physically ill patients. On its depression subscale assesses depressive symptoms such as dysphoria, anhedonia, and reduced drive, while physical symptoms of depression are purposefully avoided in order to minimize the impact of physical symptoms of organic diseases confounding depression scores. The anxiety and depression subscales each consist of 7 multiple-choice items with individually graded answering options scored 0 to 3. A cut-off value of ≥9 for the depression subscale was considered abnormal, as recommended by the manual for the German version of the scale.

Measurements of Cytokine Levels

Out of the first 356 participants, for all those who scored on the highest (≥21) or lowest (≤5) quartiles of MQ scores, serum concentrations of four different cytokines were measured in duplicate. Cytokine levels were determined using the quantitative enzyme-linked immunosorbent assay kit Fluorokine from R&D Systems according to the recommendations of the manufacturer. Plates were analysed with a Lumimex 100 analyzer. For IL-1β, the assay had a limit of detection of 0.27 pg/ml; an intra-assay coefficient of variation (CV) of 5.5%, and an interassay CV of 10.0%. For IL-6, the assay had a limit of detection of 0.36 pg/ml, an intra-assay CV of 5.2%, and an interassay CV of 10.1%; for IL-10 the detection limit was 0.13 pg/ml, an intra-assay CV of 6.4%, and an interassay CV of 10.1%. For TNFα, the detection limit was 0.47 pg/ml with an intra-assay CV of 4.3% and an interassay CV of 10.7%. All measurements were performed by laboratory personnel who were blinded to the diagnostic identity of the samples.

Statistical Methods

On study participants with complete MQ and HADS scores, descriptive statistics were conducted and presented as means ± standard deviations, medians and inter-quartile ranges, or percentages, as appropriate. Coefficients of correlations are presented as Spearman Brown’s rank correlations. Additionally, univariate analysis of variance was used to compare HADS depression scores across quartiles of IL-10. In order to identify independent predictors of depression, a set of linear regression models was calculated using an enter approach. In these models we a priori included the following co-factors: age, sex, vital exhaustion, and obesity as defined by a BMI >30 kg/m². Other potentially relevant covariates were not included, because they were unrelated to depression (eg, statin medication) or cytokine levels (eg, psychotropic medication, family history) in bivariate analyses. In order to alleviate heteroscedasticity of the non-normally distributed cytokine data, we performed Box-Cox transformations using the maximum likelihood method. In these regression models each cytokine was entered separately in order to avoid multicollinearity, which was confirmed by calculating the corresponding variance inflation factors. Finally, a regression model was computed for assessing independent predictors of depression in which all individually significant cytokines were included. All statistical analyses were performed on a personal computer using the SPSS statistical package version 18 (SPSS Inc., Chicago, Illinois, USA) for Windows. In all tests a p value <.05 was considered statistically significant.

RESULTS

Prevalence of Depressive Mood and Vital Exhaustion

The majority of participants in the presented substudy had HADS depression scores within the normal range. Forty patients (22.6%) scored above the cut-off for depression on the HADS (Table 1). Administration of psychotropic drugs as well as a family history of CHD or heart failure were significantly associated with depressive mood. As described, females more often reported on both depressive mood and vital exhaustion. No differences between depressed and non-depressed patients were found with respect to heart rate, LVEF, LVEDD, and lipid-lowering drug medication (mainly statins), respectively. There was a marginal difference in the prevalence of obesity, as the rate for a BMI >30 kg/m² was 34.5% in non-depressed and 51.4% in depressed patients, respectively (p = .069). Almost all patients with elevated HADS depression scores (97.5%) scored in the upper MQ exhaustion quartile, while patients with normal HADS...
TABLE 1
Demographic and Medical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Whole study Population (N = 177)</th>
<th>Patients without depressive symptoms (n = 137)</th>
<th>Patients with depressive symptoms (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>61.0</td>
<td>65.0</td>
<td>47.5</td>
<td>.046</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.9 ± 11.1</td>
<td>62.0 ± 11.3</td>
<td>61.4 ± 10.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>58.8</td>
<td>58.4</td>
<td>60.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3 ± 5.6</td>
<td>29.0 ± 4.5</td>
<td>30.0 ± 8.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35.6</td>
<td>32.8</td>
<td>45.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>87.0</td>
<td>85.4</td>
<td>92.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>28.8</td>
<td>29.2</td>
<td>27.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hyperlipoproteinemia (%)</td>
<td>53.1</td>
<td>52.6</td>
<td>55.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>57.3</td>
<td>55.5</td>
<td>65.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lipid-lowering drugs (mainly statins)</td>
<td>39.0</td>
<td>38.7</td>
<td>40.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychotropic drugs (%)</td>
<td>11.3</td>
<td>7.3</td>
<td>25.0</td>
<td>.002</td>
</tr>
<tr>
<td>Family history of CHD (%)</td>
<td>40.1</td>
<td>34.3</td>
<td>60.0</td>
<td>.004</td>
</tr>
<tr>
<td>Family history of heart failure (%)</td>
<td>15.8</td>
<td>12.4</td>
<td>27.5</td>
<td>.021</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>148.8 ± 26.8</td>
<td>149.3 ± 25.5</td>
<td>147.1 ± 31.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84.6 ± 14.0</td>
<td>85.2 ± 12.8</td>
<td>83.0 ± 17.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>70.2 ± 12.8</td>
<td>71.0 ± 11.4</td>
<td>67.4 ± 16.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>60.5 ± 7.8</td>
<td>60.7 ± 7.9</td>
<td>59.9 ± 7.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>LV end diastolic diameter (mm)</td>
<td>50.5 ± 5.3</td>
<td>50.7 ± 5.5</td>
<td>49.9 ± 4.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Scoring in upper MQ quartile (%)</td>
<td>60.3</td>
<td>36.5</td>
<td>97.5</td>
<td>&lt;.0005</td>
</tr>
</tbody>
</table>

Notes. CHD = coronary heart disease; LV = left ventricular; MQ = Maastricht Questionnaire.

depression scores still scored in the fourth exhaustion quartile in 36.5%.

Relationship between Cytokine Levels and Depressive Symptoms

When investigating the relationship between depressive mood and elevated serum level of cytokines, we found that higher HADS depression scores were significantly associated with elevated IL-6 concentrations (ρ = .231; p = .002). Similarly, the TNFα levels were higher in patients with high HADS depression scores (ρ = .341; p < .001). Interestingly, there was also a highly significant association between depressive mood and serum levels of IL-10 (ρ = .370; p < .001). Mean HADS depression scores differed significantly across quartiles of serum IL-10, as assessed by ANOVA (Figure 1; p < .0005). Patients from the first quartile of IL-10 showed the lowest and those from the fourth quartile showed the highest depression scores. In contrast, IL-1Β levels were not associated with HADS depression scores.

Intercorrelations among Different Cytokine Levels

In the study cohort we found that serum concentrations of IL-1β correlated positively with TNFα levels (ρ = .218; p = .004), whereas no such correlations were observed between IL-1β and either IL-6 or IL-10. IL-10 concentrations were positively related to TNFα (ρ = .416; p < .001) and IL-6 levels (ρ = .345; p < .001).

Interleukin-10 is Independently Related to Depressive Mood

Next, a set of multiple linear regression models using an enter approach were performed in the total study cohort to investigate which of the cytokines tested independently predicted depressive mood (Table 2). First, each cytokine was entered separately in addition to age, sex, vital exhaustion, and obesity. Since cytokine levels were non-normally distributed even after log-transformation, Box-Cox-transformed values were used in these analyses. In all these models, age, female sex and obesity failed to reach statistical significance, whereas vital exhaustion was always a strong and highly significant predictor of depressive mood regardless of which individual cytokine was studied (all β-coefficients >0.67;
p < .001). Serum levels of TNFα and IL-1β never reached statistical significance in predicting depressive mood. However, serum IL-10 was positively related to depressive mood independently from other clinical parameters including vital exhaustion (β = 0.165; p = .002), while the association of IL-6 with depressive mood was marginally significant (β = 0.101; p = .064). At last, we computed a regression model in which we included all cytokines as independent variables. Even in this approach elevated serum IL-10 concentrations remained a significant predictor for depressive mood (β = 0.157; p = .009), while the effect of IL-6 became nonsignificant. This loss of significance could not be explained by multicollinearity (all variance inflation factors < 1.6).

**Associations of Interleukin 6 and Interleukin10 with Depressive Mood in Exhausted and Non-exhausted Participants**

Finally, we tested subgroups of study patients with low versus high vital exhaustion scores separately for which individual cytokine there was a positive correlation to depressive mood. Also in the two subgroups of vitally exhausted and non-exhausted participants, neither IL-1β nor TNFα levels were linked to depressive mood. However, when we instead tested IL-6 and IL-10 levels for their association with HADS depression scores, we found that IL-6 was positively linked to HADS depression scores only in vitally exhausted patients (ρ = .247; p = .020), but not in patients classified to the lowest vital exhaustion quartile (ρ = .052; p = .627). The difference in correlations was marginally significant (p = .062). In contrast, IL-10 was significantly related to depressive mood in non-exhausted patients only (ρ = .262; p = .014), while in the exhausted subgroup the correlation was not significant (ρ = .113; p = .292). However, the two correlations were not significantly different from each other (p = .15).

**DISCUSSION**

In the present paper we describe that in a study cohort of primary care patients with cardiovascular risk factors and extreme scores for vital exhaustion, TNFα, IL-6 and IL-10 are all positively correlated with the presence and degree of depressive mood. This finding confirms our previously published data in the same study population40 and, furthermore, allowed us to investigate the relationship between depressive mood and elevated cytokine levels by means of subgroup analyses. The purpose of this post-hoc investigation was to test the hypothesis that in patients with cardiovascular risk factors and extreme vital exhaustion scores elevated cytokine levels are independently associated not only with mainly physical symptoms of depression (as covered by the MQ) but also with cognitive–affective symptoms of depression (as measured by the HADS).

The central finding in this study was that the anti-inflammatory cytokine IL-10 was independently associated with depressive mood. The association of IL-10 with cognitive-affective symptoms of depression was demonstrated in two different multivariate regression models, irrespective of whether this cytokine was added as a single variable or in combination with other cytokines. Moreover, we found that in the whole sample the association persisted after controlling for vital exhaustion, although cognitive–affective and physical symptoms were highly correlated. Similarly, in the subgroup of study participants with low vital exhaustion scores, elevated serum levels of IL-10 were still linked to HADS depression scores, while there
was no such association in patients from the highest vital exhaustion quartile. Since the difference between correlation coefficients in the exhausted and non-exhausted subgroup was not significant, its possible meaning needs further investigation. Nevertheless, the subgroup analyses show that even within the inhomogeneous non-exhausted subgroup, IL-10 was still related to depressive mood. In contrast, the well-described association between depression and increased IL-6 concentrations may at least in part be attributed to the fatigue experienced by many of these patients. After adjustment for exhaustion, IL-6 was only marginally related to depressive mood and subgroup analyses suggested that only in exhausted patients IL-6 has an additional impact on depressive mood. These findings confirm that depressive mood as the mainly cognitive–affective component of depression and vital exhaustion with its more physical focus are distinct psychological states with somewhat different cytokine profiles, despite their relatively high interrelation.

Due to missing experimental data, the pathophysiological role of elevated IL-10 levels in the context of depression remains unclear. IL-10 has been described as an important immunoregulatory mediator that can attenuate inflammatory responses by suppressing cytokine production and proliferation of immune-competent cells. Local IL-10 secretion limits infiltration by autoaggressive immune cells and thus prevents tissue damage produced by overwhelming immune reactions.53,54 Numerous animal studies have shown that IL-10 increases host susceptibility to a broad range of infectious microorganisms, indicating that enhanced IL-10 production may hinder the successful eradication of microbial pathogens.54–56 In patients with cardiovascular risk factors the compromised eradication of infectious pathogens may predispose the arterial intima to unbalanced inflammatory reactions.

Prolonged exposure to stress has been shown to promote arteriosclerosis possibly via elevation of arterial blood pressure and leads to a sustained and profound alteration in the cytokine network.32,34,57–58 Our observation that IL-6 and IL-10 levels are both related to particular symptoms of depression may reflect the pleiotropic actions of these cytokines. Expression of IL-10 has been detected histopathologically in a substantial number of advanced human atherosclerotic plaques, where it is localized mainly in infiltrating macrophages.59,60 These antigen-presenting cells are key players in the formation of arteriosclerotic lesions and may be the primary source for the elevated IL-10 serum levels. The up-regulated IL-10 synthesis in this patients group may help to limit tissue damage by infiltrating immune cells, but as an unfavourable side-effect it also weakens the effective eradication of various infectious agents. These immunomodulatory effects of IL-10 may account for the long-lasting neurohormonal activation in arteriosclerosis and contribute to the cognitive–affective symptoms of depressive mood in patients with various cardiovascular risk factors.38

Our finding that elevated IL-10 levels are not linked to depression in the most exhausted patients was unexpected, since we have previously reported that in the same study sample of patients with cardiovascular risk factors IL-10 is a significant and independent predictor of vital exhaustion.40 The association between the anti-inflammatory cytokine IL-10 and vital exhaustion may conceal any additional effect of depressive mood, once a certain level of exhaustion has been reached. Therefore, it is interesting to know if this cytokine will be a suitable marker for identifying depressed patients that express negative thoughts and feelings but still no somatic symptoms of depression. In contrast, IL-6 may be the “classical” pro-inflammatory cytokine which has a predictive role for depressive mood particularly in those depressed patients who additionally experience severe physical signs and neurovegetative dysregulation. In subjects with cardiovascular risk factors, ongoing and long-lasting inflammatory reactions in the vessel wall may account for the unbalanced overproduction of IL-6, which contributes to the manifestation of both physical and mental symptoms of depression. Interestingly, the functional changes resulting in diminished social participation and reduced activity levels commonly observed in depressed patients are also present in a variety of inflammatory disease conditions, in which the pro-inflammatory role of IL-6 has been well documented.8 Thus, our observation that elevated IL-6 and IL-10 secretion are both positively related to depression in subjects with cardiovascular risk factors does not contradict the assumption that each of these extracellular molecules executes its unique signaling features and modulates behavioral and mental processes in a complex and distinct manner.

LIMITATIONS

A major limitation of this study lies in the fact that cytokine levels were not determined in all study participants, as measurements were restricted to patients scoring high versus low on vital exhaustion. Furthermore, due to the cross-sectional nature of our study design, we are currently unable to draw any conclusion towards a causal relationship. The self-reported classification of study participants as being depressed was obtained by a well-validated and frequently used instrument but not confirmed by either a structured clinical interview or diagnosis by an experienced clinician. Another limitation is the moderate size and heterogeneity of our sample. Because not in all patients stress testes were routinely performed to exclude coronary artery disease, the sample may comprise an unknown number of patients with undiagnosed coronary artery disease. However, all patients had cardiovascular risk factors and were clinically well-characterized. It is most likely that the majority had some degree of atherosclerosis but none had clinical complications of coronary heart disease such as myocardial infarction or heart failure which would lead to major disturbances in mood and inflammation.
In conclusion, our data show that in patients with cardiovascular risk factors and extreme scores for vital exhaustion elevated serum concentrations of IL-6 and IL-10 are associated with the presence and degree of depressive mood. With respect to vital exhaustion the positive correlation seen between depressive symptoms and elevated cytokines may be differentially regulated in distinct subpopulations of depressed patients. However, further investigations in unselected populations with cardiovascular risk factors are warranted to test whether indeed individual cytokine profiles distinguish between different subpopulations of depressed patients.

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NOTE

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REFERENCES


