Soluble interleukin-2 receptor and tumor necrosis factor levels in depressed patients in Estonia

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Summary. *Several studies have reported immune system alterations in depressed patients. Furthermore, correlations between some interleukins and specific depressive symptoms have been found, but results are ambiguous. It might be caused by heterogeneous patient population and concomitant administration of antidepressants. The aim of our study was to look at differences in the levels of soluble interleukin-2 receptor (sIL-2R) and tumor necrosis factor-α (TNFα) between currently depressed patients with first or recurrent episode of depression, patients in full remission and healthy controls. Secondly, we looked for correlations between sIL-2R and TNFα and different depressive symptoms. A total of 75 medication-free currently depressed patients (76% of females), 17 patients in the full remission phase of major depression (58.8% of females), and 55 healthy controls (58.2% of females) participated in this study. The results showed that the level of sIL-2R was significantly lower in depressed patients in remission phase compared to the healthy controls and subjects with recurrent depression. Drug-naïve patients with major depressive disorder with recurrent episode had higher levels of sIL-2R than previously treated or patients with the first episode. TNFα levels were higher in drug-naïve patients with major depressive disorder with recurrent episode compared with previously treated patients. Further analysis of patients revealed that sIL-2R was positively correlated with decreased activity and agitation. TNFα was associated with decreased activity and suicidality.*

Introduction

The involvement of inflammatory response system (IRS) in the pathogenesis of affective disorders has become a topic of scientific debate and scrutiny. Several lines of evidence implicate the immune system as an important factor in the development of depression. A high prevalence of depressive symptoms in immune-mediated disorders including autoimmune thyroid disease and multiple sclerosis (1, 2) indicates the possible role of IRS in depression. In addition, some cytokines, such as interferon-α and interleukin-2 (IL-2), commonly used in immune therapy of autoimmune and malignant disorders are also used as a model of cytokine-induced mood disorder (3). The relationship between cytokines and sickness behavior has been further supported by experimental animal studies (4).

The exact role of the immune system in depression has been recently addressed in human studies. For example, Maes et al. (5) measured the concentrations of serum cytokines including interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), soluble interleukin-2 receptor (sIL-2R), and transferrin receptor in currently ill (n=61) and remitted (n=16) patients with major depression. Increased production of all studied biomarkers in depressive groups in comparison to healthy subjects was demonstrated. Maes et al. did not find a significant difference between patients who were in an acute phase of illness or in complete clinical remission. In contrast, Mikova et al. (2), albeit with a smaller sample, did not demonstrate any difference in IL-2 receptor concentrations in their smaller sample between depressive patients (n=28) and healthy controls (n=15). However, higher levels of tumor necrosis factor-alpha (TNFα) were observed among patients. More recently, Kahl et al. (6) demonstrated higher levels of both TNFα and IL-6 in currently depressed medication-free female patients (n=12) with borderline personality disorder as compared with healthy controls (n=12). It is notable that serum TNFα levels were also positively correlated with Beck Depression Inventory (BDI) scores in healthy women (7), but

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negatively correlated with severity of depression in depressed children (8), suggesting that involvement of cytokines in depression is more complex than quantitative alterations. Recently, Simon et al. (9) could not find differences in the TNFα system between depressed patients and healthy controls; however, several cytokines, including IL-2, were significantly elevated in a sample of patients. There is evidence that an elevation of TNFα level might be an early predictive marker for weight gain during treatment with psychotropic medication, but results are conflicting. Hienze-Selch et al. (10) showed this association in treatment with tricyclic antidepressants but not with paroxetine. Kraus et al. (11) found an analogous association for mirtazapine and venlafaxine treatment. Contrarily, Himmerich et al. (12) did not find associations between TNFα, weight, body mass index (BMI), and also weight gain during antidepressive treatment.

The population of depressive patients is heterogeneous; patients experience a wide variety of symptoms despite having the same diagnosis. Different subtypes of depressions might have distinct immune patterns such as melancholic versus nonmelancholic depression. For example, Kaestner et al. (13) found higher interleukin-1 beta and interleukin-1 receptor antagonist levels in melancholic (n=21) versus nonmelancholic patients (n=16). Furthermore, Schlatter et al. (14) also demonstrated a higher CD4+ lymphocyte subset in melancholic (n=14) versus nonmelancholic patients (n=28), but did not find any differences in IL-2 levels. In addition, Rothermundt et al. (15) showed that nonmelancholic patients had increased monocyte counts and α2 macroglobulin. However, Marques-Deak et al. (16) did not detect significant differences between melancholic (n=28) and nonmelancholic (n=18) patients when comparing levels of IL-1β, IL-6, interferon-gamma, or cortisol.

Taken together, the available data are rather inconsistent or controversial and do not allow clear conclusions to be drawn regarding involvement of cytokines in depression. Most of the mentioned studies were limited by small or heterogeneous samples, whereas additional bias might be caused by concomitant use of antidepressive medications during the measurement of cytokines. Moreover, only few of the previous studies have addressed the association between cytokines and specific symptoms of depression or different stages of clinical course. In order to highlight these aspects, our study aimed to clarify further the relationship between depression and two of the most common biomarkers – sIL-2R, a T-cell activation marker, and TNFα, mostly from the macrophage system. The fact that different cells can produce these cytokines may indicate their unique or distinct role in the pathogenesis of depression. Possible effects of cytokine alterations on the brain functioning and the pathogenesis of depression were described in a recent review by Schiepers et al. (17). In particular, we aimed to measure the serum concentrations of sIL-2R and TNFα cytokines in three depressive groups with the first and recurrent episodes and remission, respectively, in comparison to healthy subjects. Additionally, we proposed to investigate the associations between serum levels of these cytokines and distinct depressive symptoms. As we have suggested, the inclusion of patients at different clinical stages in the study and more detailed focus on the depressive symptomatology should shed better light on the role of cytokines in depression.

Material and methods

Subjects

The study cohort consisted of 75 currently depressed subjects (mean age, 36.5±12.7 years; 76%, females; 50.7%, drug-naïve patients) and 17 patients in full remission (mean age, 35.8±14.5 years; 58.8%, females) recruited from the Clinic of Psychiatry of Tartu University, and 55 healthy controls (mean age, 32.7±15.0 years; 58.2%, females) from the same geographical area. The diagnosis of major depression according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria was verified by using the Mini International Neuropsychiatric Interview (MINI 5.0.0). After a standardized diagnostic interview MINI 5.0.0, severity of depressive symptoms was assessed both by the Hamilton Depression Scale (HAM-D) and the BDI. All subjects with mild depressive symptoms with the HAM-D score of less than 20 were excluded from the study. For healthy subjects and for patients in full remission, the HAM-D score was less than 9. The exclusion criteria were severe substance abuse, acute infections, neurological or immunological disorders, bipolar depression, and panic disorder. Participants did not receive any antidepressive treatment for at least two weeks, and the intake of anti-inflammatory drugs including steroids was not allowed, with the exception of hormonal contraceptives. If previous episodes were treated, then antidepressants from different classes, but not antipsychotics, lithium, or anticonvulsants, were used. Patients could meet the criteria of generalized anxiety disorder if this was not dominant. Full remission was defined as at least six months of euthymic period without antidepressive treatment. Patients

were physically healthy and did not receive physical therapy.

The healthy subjects were interviewed using the MINI 5.0.0 and were questioned about personal and family psychiatric history. They were physically healthy and did not receive therapy. A positive history of psychiatric disorders in the first-generation relatives was an exclusion criterion for healthy subjects. Table 1 includes demographic data for all participants. There were no significant differences in age, sex, or BMI between the study groups. Smoking habits were assessed as the amount of cigarettes smoked per day within the last 6 months: 0, no cigarettes; 1, 1–2 cigarettes per day; 2, 3–10 cigarettes per day; 3, 11–20 cigarettes per day; and 4, more than 20 cigarettes per day. There were 49.0% of smokers (at least 1 cigarette per day) in the recurrently depressed patient group, 18.2% in the first episode group, 28.6% in the full remission group, and 32.0% in the healthy controls. However, the differences were not statistically significant (χ^2=5.89; *P*=0.117).

All subjects gave informed written consent, and approval was granted by the Human Studies Ethics Committee of Tartu University.

Procedure

A blood sample of 7 cm^3 was collected between 9.00 AM and 11.30 AM in the morning. After complete clot formation, the samples were centrifuged, and serum was divided. Serum sIL-2R and TNFα were analyzed on the day the blood sample was collected, without freezing the probes. A solid-phase, enzyme labeled, chemiluminescent sequential immunometric assay was carried out on an IMMULITE analyzer (Diagnostic Product Corporation, Sweden). The intra-assay coefficient of variation for sIL-2R was 3.7%, for TNFα 3.6%; the inter-assay coefficients were 8.1% and 6.5%, respectively.

Data analysis

The comparison of demographic data between the groups was performed with the Fisher's exact test for gender and existence of melancholic symptoms, and with the Kruskal-Wallis test for age and BMI. We used ANOVA with post hoc analysis to compare scores of HAM-D and BDI, and biomarkers between all studied groups. The Student's *t* test was used to compare currently euthymic and dysthymic subjects or else melancholic and nonmelancholic patients. As sIL-2R and TNFα did not follow Gaussian distribution, we used logarithms to normalize the data. Seventeen measurements of TNFα (11.6%) were below the level of 4 ng/L, and this was considered in analyses. We used multiple regression analyses to find out associa-

Table 1. **The demographic data of study cohort, the mean scores of HAM-D and BDI with statistical comparisons**

Characteristic	FE	RE	FR	HC	*P* value
Male/female	4/8	14/49	7/10	23/32	*P*=0.123*
Age, mean (SD), years	32.50 (14.28)	37.24 (12.35)	35.76 (14.54)	32.75 (14.10)	*P*=0.150**
BMI, mean (SD), kg/m^2	25.38 (4.02)	22.22 (3.24)	22.99 (2.90)	24.15 (4.47)	*P*=0.176**
HAMD score, mean (SD)	24.27 (4.54)	24.14 (3.11)	3.19 (3.54)	1.08 (1.22)	***F*=760.061*** ***P*=0.00******
BDI score, mean (SD)	30.40 (7.88)	30.08 (8.86)	4.85 (3.98)	4.32 (4.81)	***F*=116.517*** ***P*=0.00*******
Melancholic symptoms, Yes/No	8/4	56/7			***P*=0.050***

FE, depressed patients with the first episode; RE, depressed patients with recurrent episode; FR, depressed patients in full remission; HC, healthy controls; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory.

*Fisher's exact test.

**Kruskal-Wallis' test.

***Group effect of ANOVA.

****Post hoc for HAM-D: FE/RE (*P*=0.889), FR/HC (*P*=0.008), FE/HC (*P*=0.000), FE/FR (*P*=0.000), RE/HC (*P*=0.000), RE/FR (*P*=0.000).

*****Post hoc for BDI: FE/RE (*P*=0.894), FR/HC (*P*=0.812), FE/HC (*P*=0.000), FE/FR (*P*=0.000), RE/HC (*P*=0.000), RE/FR (*P*=0.000).

tions between sIL-2R, TNFα and scores of BDI, HAM-D, age, sex, BMI, and smoking habit. The correlation between IL-2R and TNFα was assessed with the Spearman's correlation analysis. We tested associations of sIL-2R and TNFα with the items of HAM-D in separate regression analyses for each cytokine and HAM-D item. We used software package R 2.4.0 – A Language and Environment.

Results

First, we compared sIL-2R and TNFα in the four study groups. As IL-2R was not correlated with age, sex, and BMI, ANOVA was conducted. The results showed a significant difference in the level of sIL-2R between the groups (Table 2). In post hoc analysis with Bonferroni correction, there were lower levels of sIL-2R in the full remission (FR) group compared with the recurrent depressive episode (RE) group and the healthy controls (HC). There was a trend towards a lower level of sIL-2R in the FR group compared to the first episode (FE) group. Previous usage of antidepressants did not influence these results (data not shown).

TNFα was correlated with BMI (but not with age and sex), and we used BMI as a covariate when analyzing this biomarker. We did not find differences in the levels of TNFα when assessing all four groups (Table 2), but comparing currently euthymic subjects (HC and FR groups) and depressed subjects (FE and RE groups) using the Student's *t* test, there were lower levels of TNFα in currently depressed subjects (t=2.193; P=0.0299). The subjects who received antidepressive treatment previously had significantly higher levels of TNFα than drug-naïve patients or HC (F=4.541; df=3; P=0.012 for 3 groups). The HC did not differ from drug-naïve patients.

To examine the effect of previous treatment, FE, drug-naïve RE, and non-drug-naïve RE patients were compared using ANOVA. The group-effect was significant for both biomarkers (for sIL-2R, F=3.67, df=2, P=0.0304; and for TNFα, F=3.707, df=2, P=0.0294). In post hoc analyses, sIL-2R levels were higher in the RE group with previous antidepressive treatment than in the drug-naïve RE group (P=0.0209) and higher in the non-drug-naïve RE group as compared with the FE group (P=0.0315). The RE group with previous antidepressive treatment had higher TNFα levels than the drug-naïve RE group (P=0.0114), but there was no statistically significant difference between other groups.

Analysis of HAMD and BDI scores by ANOVA revealed significant group differences (Table 1). There was no difference in the HAMD scores between the FE and RE groups; the differences between the FR and HC, FE and HC, FE and FR, RE and HC, and RE and FR groups were significant (post hoc test). There were no differences in the BDI scores between the FE and RE groups and between the FR and HC groups; other differences were statistically significant (post hoc test).

Regression analysis demonstrated a significant positive association between HAM-D scores and TNFα (β=0.041; P=0.041), but not sIL-2R (β=0.028; P=0.158) levels in currently depressed patients. The levels of both biomarkers did not correlate with BDI scores (for TNFα, β=0.007, P=0.396; for sIL-2R, β=0.004, P=0.589), with the number of depressive episodes, or with the duration of current episode (data not shown). Smoking habits were also not associated with cytokine concentrations (for IL-2R, β=0.063, P=0.413 and for TNFα, β=0.010, P=0.749). In the group RE, more patients had melancholic symptoms than in the FE group (Table 1), but there was no association between melancholia and cytokines (for IL-2R, F=1.225, df=1, P=0.274; and for TNFα, F=0.065, df=1, P=0.799). The concentrations of

Table 2. **The concentrations of interleukin-2 receptor (IL-2R) and tumor necrosis factor-alpha (TNFα) in study groups with statistical comparisons in ANOVA**

Marker	FE	RE	FR	HC	*F*	*df*	*P* value
IL-2R, mean (SD), kU/L	431.75 (111.24)	506.90 (174.06)	354.94 (142.78)	453.55 (136.10)	5.462	143	0.001*
TNFα, mean (SD), ng/L	5.48 (1.72)	6.46 (3.16)	7.72 (3.74)	7.29 (3.56)	2.441	90	0.052

FE, depressed patients with the first episode; RE, depressed patients with recurrent episode; FR, depressed patients in full remission; HC, healthy controls.

*Post hoc for IL-2R: FE/RE (P>0.05), FR/HC (P=0.004), FE/HC (P>0.05), FE/FR (P=0.080), RE/HC (P>0.05), RE/FR (P=0.0001).

IL-2R and TNFα did not correlate (Spearman's r=0.079, P=0.345).

To establish the associations between individual symptoms and cytokines, we conducted separate regression analyses on the currently depressed subjects including, one by one, all items of HAM-D. The data were adjusted for BMI for TNFα. IL-2R levels were related to two items: decreased activity (the seventh item of HAM-D, β=0.259, P=0.026) and agitation (the ninth item of HAM-D, β=0.284, P=0.018). TNFα levels were associated with decreased activity (β=0.294; P=0.013) and suicidality (the third item of HAM-D, β=0.152, P=0.025). IL-2R and TNFα levels were not related to any BDI items.

Discussion

The first finding of our study was significantly decreased levels of sIL-2R in patients with full remission. The higher levels of both sIL-2R (5, 18) and IL-2 (14) were previously demonstrated in currently depressive patients by different research groups. In addition, the elevation of these cytokines has also been described in schizophrenia (19). The sIL-2R is a marker of T-cell activation. Maes et al. (5) reported that sIL-2R concentrations appeard to correlate with IL-2 secretion, and higher levels of sIL-2R might suggest up-regulated production of IL-2. If so, then patients with major depressive disorder (MDD) in remission phase have lower T-cell activation than other groups in our study cohort, and this finding may suggest to the secondary adaptive changes of immune system activity in remission phase of MDD. Interestingly, it has been recently shown that sIL-2R levels decrease in thyroid autoimmunity after thyroxin treatment withdrawal, even below those of healthy euthyroid controls (20). However, the group of patients in full remission was quite small, suggesting that further investigations are needed.

Secondly, the levels of TNFα were higher in case of previously untreated recurrent depression. The levels of TNFα seem to be a state marker as it was found in many previous studies. There is evidence that TNFα regulates serotonin uptake (21) and probably acts differently in various stages of disturbance (22). Increased levels of TNFα have often been found in depressive patients compared to healthy controls (23, 24). In contrast, Simon et al. (9) did not find differences in TNFα levels between patients with major depression and healthy controls. Although we did not find differences in TNFα levels comparing four study groups, we found that previous antidepressive treatment has an impact on TNFα levels. This may be an important reason why different studies get different results in that field. In previously treated patients, the reduction of TNFα may be a compensatory reaction of the immune system. There are opposite results: Kagaya et al. (25) demonstrated an increase in TNFα concentration during treatment; Lanquillon et al. (26) found a decrease in TNFα concentration in responder group during the treatment with amitriptyline; Tuglu et al. (24) reported a decline of TNFα after a 6-week treatment with different selective serotonin reuptake inhibitors. There are data that TNFα levels are significantly lower in remitted patients receiving maintenance antidepressive treatment for longer than 6 months in comparison to healthy controls (27). The data are confusing. Probably, different antidepressants have a different impact on immune system reaction, and there are no data about time-pattern of these immunological reactions during and after antidepressive treatment. Suarez et al. (7) have demonstrated associations between TNFα and higher BDI scores. We found a positive correlation between HAMD and TNFα in currently depressed subjects, but not in euthymic individuals. This finding is in accordance with previous studies (28) and supports the hypothesis of compensatory mechanism, as more severe depression correlates with less decreased levels of TNFα.

Furthermore, we were interested in associations between studied cytokines and single symptoms of depression. We found positive correlations between sIL-2R, decreased activity and agitation. Therefore, it may be that psychomotoric symptoms are influenced by T-cell immunity. In addition, it has been described that IL-2 has an immense effect on the dopaminergic neurotransmission (22), which is related to psychomotoric symptoms.

Significant positive correlations were found between TNFα, suicidality and decreased activity. Reichenberg et al. (29) have reported an association between TNFα and food consumption. In animal studies, association between TNFα and sexual behavior has been reported (30). We applied the HAM-D and the BDI and could not demonstrate such correlations. Possibly, more specific scales or behavioral methods are needed for assessing the relationship between TNFα and sexual symptoms or food consumption. As TNFα was correlated with certain symptoms of depression, it is possible that an increase in the TNFα level is related to some specific subpopulation of depressive disorder, but this requires further research.

There are several limitations in our study. First, we measured inflammatory markers only once, before treatment. It would be useful to measure the concentrations repeatedly throughout the treatment for better dynamic characterization. Secondly, as all the samples were not analyzed together, there could be some difference in used reagents. At the same time, the procedure we used guaranteed the analysis of fresh samples. Thirdly, the required duration of remission phase was at least 6 months of euthymic mood without antidepressive treatment, but the exact duration of remission and drug-free period was not measured. Additionally, the group of remitted patients was relatively small, which may lead to false positive results.

Conclusions

Lower levels of sIL-2R in depressive patients in the remission phase may be the sign of lowered T-cell activity in this phase of disorder. The recurrence of major depressive disorder is associated with increased levels of sIL-2R in drug-naïve patients. Previous treatment has an impact on TNFα concentrations and immune system activity. Drug-naïve patients with major depressive disorder with recurrent episode had significantly higher levels of TNFα levels than previously treated patients. We confirmed that distinct depressive symptoms were correlated with different inflammatory markers. TNFα was related to severity of depressive symptoms in currently depressed patients. However, it would be no doubt useful to examine the impact of treatment on changes in symptom severity in relation to inflammatory markers in further research.

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Estijos sergančiųjų depresija tirpaus interleukino-2 receptoriaus ir naviko nekrozės faktoriaus kiekis

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Raktažodžiai: depresija, citokinai, tirpus interleukino-2 receptorius, naviko nekrozės faktorius α.

Santrauka. Įvairiais tyrimais nustatyti sergančiųjų depresija imuninės sistemos pažeidimai. Be to, nustatytas tarpusavio ryšys tarp kai kurių interleukinų ir specifinių depresijos simptomų. *Tyrimo tikslai.* Tačiau rezultatai liko neaiškūs. To priežastis gali būti pacientų heterogeniškumas ir kelių antidepresantų poveikis. Pirma: išaiškinti tirpaus interleukino-2 receptoriaus (sIL-2R) ir naviko nekrozės faktoriaus α (TNFα) kiekio skirtumus tarp sergančiųjų depresija (pirmuoju ar pasikartojančiu depresijos epizodu), visišką remisiją pasiekusių pacientų ir kontrolinės grupės tiriamųjų. Antra, nustatyti ryšį tarp sIL-2R bei TNFα ir skirtingų depresijos simptomų. Šiame tyrime dalyvavo 75 vaistais negydomi depresija sergantys pacientai (76 proc. moterų), 17 pacientų, pasiekusių didžiosios depresijos visiškos remisijos fazę (58,8 proc. moterų), ir 55 sveikų tiriamųjų kontrolinė grupė (58,2 proc. moterų). Tyrimo rezultatai parodė, kad sIL-2R kiekis buvo gerokai mažesnis ligos remisijos fazę pasiekusių pacientų grupėje nei kontrolinės grupės ir tiriamųjų pacientų, sergančių atsikartojančia depresija grupėje.

Nustatyta, jog vaistais negydytiems depresija sergantiems pacientams, su atsikartojančiu depresijos epizodu, būdingas didesnis sIL-2R kiekis nei prieš tai gydytiems pacientams ar pacientams, sergantiems pirmuoju epizodu. TNFα kiekiai gydymo negavusių pacientų su atsikartojančiu depresijos epizodu grupėje buvo didesni palyginti su gydytais pacientais. Tolesnis pacientų tyrimas parodė esant teigiamą sIL-2R koreliaciją su sumažėjusiu aktyvumu ir nerimu. TNFα buvo siejamas su sumažėjusiu aktyvumu ir suicidiškumu.

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