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ORIGINAL PAPER

IL-1β, IL-6, IL-8, IL-10, IFN-γ, TNF-α and its relationship with lipid parameters in patients with major depression

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Abstract There is some evidence that an immune response with an increased production of proinflammatory cytokines frequently accompanies major depression. The aim of this study was to determine the serum levels of interleukines (IL-1β, IL-6, IL-8, IL-10), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and immonuglobulines (IgG, IgA and IgM) levels and to examine the relationships between all above parameters and lipid parameters. The study group included 30 patients and 30 healthy volunteers. Although total cholesterol, HDL-cholesterol, and IgM levels were increased significantly ($p<0.05$) in patients and compared to those of the controls, no statistically significant differences ($p>0.05$) were observed with other parameters. IFN-γ were positively correlated with total cholesterol ($r=0.425$; $P=0.019$) and LDL-cholesterol ($r=0.391$; $P=0.032$) levels in patients. Other cytokines and immunoglobulins did not show any correlation with lipid parameters. It was concluded that although no differences was observed in cytokines and immunoglobulin levels in the present study, the dysregulation of the lipids and immune system including the cytokine network is associated with the etiology and pathophysiology of major depressive disorders.

Keywords Cytokines · Immunoglobulins · Lipids · Major depressive disorders

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There is strong evidence that the immune system and the central nervous system communicate bidirectionally via hormones, neurotransmitters and peptides (Tuglu and Kara 2003). It is known that cytokines are endocrinologically, electrophysiologically, and behaviorally active (Turnbull and Rivier 1999). Cytokines secreted by peripheral leukocytes can cross the blood-brain barrier. Central and peripheral administration of cytokines induce fever and sleep; and alter eating behavior, locomotor and exploratory behavior, and mood states (Connor and Leonard 1998; Maier and Watkins 1998). Cytokines influence the hypothalamic-hypophyseal-adrenal axis (HPA) by direct inhibition of the synthesis of **C**-reactive protein (CRP) and indirect induction of glucocorticoid receptor resistance (Bousquet et al. 2000; Tuglu and Kara 2003; Kyrou et al. 2006). In addition, they induce the release of neurotransmitters from neurons in various regions of the brain (Maes et al. 1993). Cytokines influence the corticotropin releasing hormone (CRH) by directly acting on the HPA axis or indirectly by interfering with its feedback. The HPA axis combined with CRH hyperactivity are responsible for early stage behavioural variabilities (Phillips et al. 2006; Bao et al. 2008). There are progressively increasing studies concerning the measurement of cytokine levels in bodily fluids and their significance on the diagnosis of major depression (Schiffer 1990; Angele and Faist 2002). In line with the cytokine hypothesis of depression, the increase in the plasma concentrations of the pro-inflammatory cytokines (e.g. IL-1 and IL-6) observed

in patients suffering from depression seems to correlate with the severity of this psychiatric disorder as well as HPA axis hyperactivity (Maes et al. 1993; Maes 1999). Cumulative evidence suggest that immunological activation and hypersecretion of proinflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-alpha may have a causal relationship with the etiology of depression (Grippo and Johnson 2002; Maes 2008). Inflammation and stress induce cytokine production (Mullington et al. 2001; Glaser and Kiecolt-Glaser 2005). Some symptoms associated with depression are observed in diseases in which cytokine levels rise (Katayama et al. 2001; Michalec et al. 2002).

Lipid mediators are important endogenous regulators of neural cell proliferation, differentiation, oxidative stress, inflammation, and apoptosis (Farooqui 2009). Several cohort studies (on nondepressed subjects) have assessed the relationship between plasma cholesterol and depressive symptoms with contradictory results. Though some results found a significant relationship between a decrease of total cholesterol and high scores of depression, some other did not. Besides, some trials showed that clinical recovery may be associated with a significant increase of total cholesterol (Partonen et al. 1999; Joynt et al. 2003). Studies among patients suffering from major depression signalled more constantly an association between low cholesterol and major depression (Colin et al. 2003; Lehto et al. 2010a). Total cholesterol, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) levels were markedly lower when amongst depressed patients when compared with the controls (Ebesunun et al. 2012). On the contrary, Das et al. (2010) found the elevared serum total cholesterol in depressed patients. It was reported that there is an inverse association of serum cholesterol concentrations with platelet serotonin uptake velocity, and low cholesterol could increase serotonin reuptake velocity in the brain, and thereby contribute to depression (Khalid et al. 1998). Numerous studies have reported that the connection of reduced serum cholesterol and thrombocyte serotonin concentration with suicidal behavior in depressed patients (Almeida-Montes et al. 2000). In the group of depressed patients with attempted suicide, statistically significant lower serum cholesterol values and in the group of depressed patients with no suicide attempt, statistically significant lower values of thrombocyte serotonin have been confirmed (Ruljancic et al. 2011).

T-lymphocytes and interferon-gamma (IFN-gamma) contribute to leukocyte recruitment in postcapillary venules during hypercholesterolemia. T-cell–derived cytokine IFN-γ as mediators of the endothelium-dependent arteriolar dysfunction caused by hypercholesterolemia (Stokes et al. 2007). A large number of cytokines including TNF, the interleukins, and the interferons increase serum triglyceride levels. The cytokines induce marked changes in lipid metabolism that lead to hyperlipidemia which represents part of the innate immune response (Feingold et al. 1998).

Because of the conflicting results of the lipid in depressed patients, and the effects of cytokines on psychiatric disorder and lipid metabolism, we want to focus on these subjects.

The goals of this study are (1) to determine the levels of IL-1β, IL-6, IL-8, IL-10, TNF-α, INF-γ, total cholesterol, triglycerides, HDL-C, LDL-C, IgG, IgA, and IgM in the sera of depressed patients, (2) to determine whether these levels differ between patients with major depression and healthy controls, and (3) to investigate the relationships between these variables, in patients with major depression.

Methods

Study population

The study group consisted of 30 patients with major depression (6 males and 24 females, mean age 38±13 years). The control group had the same number of subjects (16 males and14 females, age 30±9 years).

The sample group comprised patients with major depression, who applied to the Psychiatry Polyclinic, Faculty of Medicine, Karadeniz Technical University. The study was approved by the local ethics committee and informed consent was obtained from the participants after all procedures were fully explained. The patients were between 18 and 65 year of age. In the psychiatric evaluations of the patients and the control group, Structured Clinical Interview for DSM-IV was used. Cases to be included in the study were evaluated by Axis 1 of the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The following categories of patients were excluded from the study group: Supplemental diagnosis of axis one disorder, psychotic or seasonal affective disorder, scoring <15 out of 17 of the Hamilton Depression Rating Scale, scoring <17 on the Beck Depression Inventory, psychotic disorders, dementia, history of psychiatric illness/psycho-active medicine use within the preceding 6 months, insufficient education to understand the test, and mentally/socially retarded cases. The study participants were instructed not to take any medication that might affect the immune system or lipid metabolism 1 month before blood was taken. The control group was derived from the hospital staff and their relatives who did not have any history of cardiac and psychiatric disorder, and who accepted to participate in the study voluntarily after being informed about the aim and reasons for the study. The control group matched the study group for age, gender and education. All participants completed the study.

Measures

Sociodemographic data collection form

This form, which was completed by all participants, was designed to gather information on age, education, gender, marital status, economical status, and the duration of the illness.

Biochemical analysis

10 mL of venous blood was drawn from each subject after a 12-h overnight fast. The blood was transferred into tubes without anticoagulants and centrifuged at 3000 rpm for 10 min. All sera samples were stored at –80 °C until use. The levels of serum glucose, total cholesterol (TC), triacylglycerol (TG), HDL-C, and LDL-C were determined by enzymatic methods using the Roche Diagnostics Modular DP analytic system (Germany). The levels of Ig A, Ig G, Ig M were determined by immunonephelometry (Dade Behring, BN II). IL-1β, IL-6, IL-8, IL-10, TNF-α, and IFN-γ levels in the samples were measured by commercial ELISA kits, all provided by The Invitrogen Corp. (Camarillo, CA), except for IFN-γ, which was supplied by Biosource International Inc. (USA).

Statistical analysis

Data were expressed as the mean plus/minus the standard deviation (SD). The distribution of variables in the study and control groups was assessed by Kolmogorow-Smirnov test, and, where shown, normal distributions were compared by parametric tests including Student's *t*-test. All parameters, except for triglycerides, IL-8, IL-10, TNF-α and IFN-γ levels (Mann Whitney *U*-test) were evaluated by Student's *t*-test between patients and control subjects. Relationships among variables were assessed by means of Pearson's or Spearman's correlations.

Results

The demographic data concerning the two groups is given in Table 1. The levels of glucose, lipid and lipoprotein parameters, immunoglobulins, cytokines parameters in patients with major depression and in control groups are shown in Table 2. Total cholesterol, HDL-C, and IgM levels in patients with major depression were significantly higher than those of the control group ($P<0.05$). Other parameters did not show any statistically significant differences between study groups ($p>0.05$). Only IFN-γ was significantly correlated with lipid parameters (with total cholesterol ($r=0.425$; $P=0.019$) and LDL-C ($r=0.391$; $P=0.032$), Figures 1 and 2 respectively) patients with major depression. On the other hand, IFN-γ was also positively correlated with TNF-α levels ($r=0.549$; $P=0.002$) (Data was not shown).

Table 1 The demographics of the study participants

	Study group	Control group
n	30	30
Age (years) (x±S.D.)	38±13	30±9
Gender (female/male)	24/6	14/16

Key: *n* number of subjects in the group; *x* mean; S.D., standard deviation

Discussion

In this study, while the atherogenic lipid parameters and the levels of IgM were significantly higher in patients than those of the controls, there was no significant difference in the levels of the cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α (although increased), INF-γ) measured in both groups.

Himmerich et al. (2008) found the elevated level of TNF-α and suggested that an activation of the TNF-α system may contribute to the development of a depressive disorder. On the other hand, Brambilla and Monteleone (2004) did not found any significant difference in TNF-α and IL-1β levels in adolescent children with major depression (MD) and explained that alternatively, the immune hyperactivity is not a phenomenon preceding the MD but develops along its course. IL-1β level was not significantly associated with depressive symptom severity (Lyness et al. 2001). But Weizman et al. (1994) obtained depressed levels of IL-1β. Huang and Lee (2007) showed that after age and body mass index (BMI) adjustments, there were no significant differences in serum IL-1β, TNF-α, and IL-10 levels between patients with MD and healthy controls, and concluded that serum TNF-α, IL-1β level and IL-1β/IL-10 ratio might play an important role in the psychopathology of acute-phase MD. Choi and Suh (1998) found no significant differences in IL-1β and IL-6 production between the female patients with MD and the healthy controls and suggested the decreased immune function is highly related to the hyperactivity of the HPA axis. Podlipný et al. (2010) reported that the participants with a very high level of self-reported symptoms of depression had a significantly lower serum level of IL-6 than the participants with a very low level of self-reported symptoms of depression. But, according to the research of Loftis et al. (2010); the levels of mitogen induced mononuclear cell pro-inflammatory cytokine (e.g. IL-1β, IL-6, TNF-α, INF-γ) secretion and their corresponding receptors are elevated in MD patients. Lehto et al. (2010b) explained that the lowered IL-8 levels in the MD group could reflect a

Table 2 Serum lipids, immunoglobulins, and pro-inflammatory cytokins levels in patients with major depression (n=30) and control subjects (n=30)

	Control	Major Depression	P^a value
Glucose (mg/dL)	82±7	86±7	NS[b]
Total Cholesterol (mg/dL)	169±33	188±31	<0.05
Triglycerides (mg/dL)	110±61	103±44	NS[b]
HDL-cholesterol (mg/dL)	49±9	59±12	<0.05
LDL-cholesterol (mg/dL)	108±33	116±29	NS[b]
IgG (mg/mL)	1252±224	1336±248	NS[b]
IgA (mg/mL)	175±80	217±85	NS[b]
IgM (mg/mL)	116±39	148±60	<0.05
Il-1β (pg/mL)	3.52±0.64	3.55±0.81	NS[b]
IL-6 (pg/mL)	5.94±1.34	5.94±1.75	NS[b]
IL-8 (pg/mL)	37.99±14.06	42.46±27.17	NS[b]
IL-10 (pg/mL)	10.22±2.25	10.55±4.79	NS[b]
IFN-γ (pg/mL)	7.49±5.89	5.83±2.93	NS[b]
TNF-α (pg/mL)	2.18±1.92	3.12±2.80	NS[b]

Values are mean±SD

[a]Statistical analysis by Student's t-test, except triglycerides, IL-8, IL-10, IL-1 β, TNF-α by Mann-Whitney U test

[b]NS, not significant

shift towards pro-inflammatory IL-8 activity that at least some of the chemokines may be down-regulated.

As seen above there has been conflicting findings in literatures. Some support us, some do not. These differences may come from methodological or the subjects properties. Today most of people life is full of stress because of their living conditions. Sometimes people feel themselves under depression. But many people attempt to show himself in a normal psychology. Psychological stress affects the immune system. Therefore, the cytokines levels of control groups (non major depressive subjects) might be affected from subjects under stress. The results may be affected from other hidden health problems of control subjects or depressive patients.

In the current study, IFN-γ was significantly correlated with TNF-α levels (r=0.549; P=0.002) and lipid parameters (with total cholesterol (r=0.425; P=0.019) and LDL-C (r=0.391; P=0.032). IFN-γ is known to be a pro-inflammatory and also anti-inflammatory cytokine. Vila-del Sol et al. (2008) reported that IFN-γ-induced TNF- α expression is regulated by interferon regulatory factors 1 and 8 in mouse macrophages. It stimulates foam cell formation by inducing cholesterol uptake and reducing cholesterol efflux and therefore promotes an imbalance in cholesterol homeostasis (McLaren and Ramji 2009). IFN-γ is a major factor contributing to hypercholesterolemia-induced arteriolar dysfunction in vivo (Ludewig et al. 2000). In the majority of studies, total cholesterol levels have been found to be lower in the clinically depressed than those of the control subjects (Olusi and Fido 1996; Maes et al. 1997; Rafter 2001). In some other studies, no correlation was established between MD and serum cholesterol levels (Oxenkrug et al. 1983; Almeida-Montes et al. 2000).Unlike some studies found the elevated

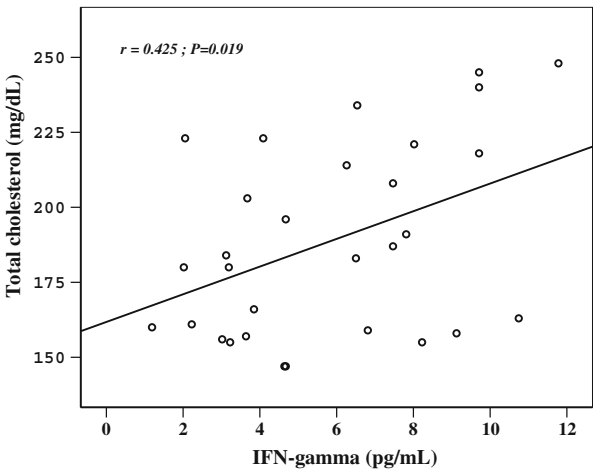

Fig. 1 The relationship between serum INF-gamma and total cholesterol in patients with major depression

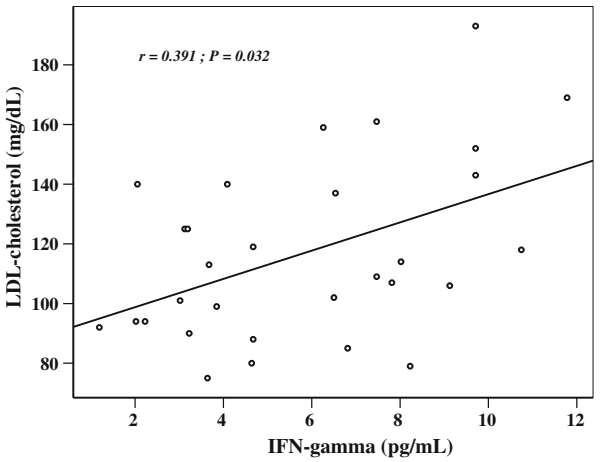

Fig. 2 The relationship between serum INF-gamma and LDL-cholesterol in patients with major depression

serum total cholesterol in depressed patients (Das et al. 2010; Kirpinar et al. 1998). Yary et al. (2010) reported that severe depressive symptoms are independent risk factors for acute myocardial infarction and the higher levels of total cholesterol was associated with individuals exhibiting severe depressive symptoms. We found cholesterol and HDL-C levels to be significantly higher in MD cases than controls. This increasing cholesterol is a risk for cardiovascular disorders for depressive patients.

Blood glucose levels were within the normal range in all study participants in our study. Brain glucose utilization is redistributed in subjects with depressive disorders. The brain's energy needs increase with psychological challenge and decrease during sleep (Schweiger et al. 2008). Some studies reported glucose tolerance defects in depressed patients (Winokur et al. 1988; Musselman et al. 2003). For instance, MD is more likely in patients with type II diabetes (Katon et al. 2005; van Steenbergen-Weijenburg et al. 2011). One of the causes of this could be the inefficiency of insulin to facilitate cellular uptake and storage of magnesium (Nadler et al. 1992). If there is insulin resistance then the storage of magnesium is blocked, thus allowing its excretion by urine. It is known that magnesium deficiency could precipitate depression (Lima et al. 2005; Barragan-Rodríguez et al. 2007; Eby and Eby 2010). On the other hand, Winters et al. (2005) did not observe any correlation between blood glucose level and depression scores. This study supports our finding. We suggested that although glucose is very important for brain, blood fasting glucose level may not be affected.

Our results indicate that total cholesterol, HDL-C, and IgM levels were increased significantly in patients and compared to those of the controls. We also found that no statistically significant difference in the levels of the cytokines measured in both groups. It was concluded that although no differences was observed in cytokines and immunoglobulin levels in the present study, the dysregulation of the lipids and immune system including the cytokine network is associated with the etiology and pathophysiology of major depressive disorders.

There are some limitations in this study. The study group was small and from the same centre; it was not cross-sectional. However, because of the inclusion of a control group, we believe that our study, despite its limitations, will serve as a guide in the conduction of further large scale studies.

In conclusion, the biomarkers of the diagnosis, therapy and prognosis of depression remain poorly understood. For this reason, new etiologic models are required for the explanation of the pathophysiology of depression.

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Conflict of Interest All authors have no conflict of interest regarding this paper.

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