

## Original Article

## Correlation between major depressive disorder and circulating natural killer cells

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### Abstract

**Background:** Major depressive disorder is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. Depression is associated with multiple immunological disorders. Aim of the present study was to determine correlation between percentage of circulating NK cells and major depressive disorder. **Materials and Methods:** Patients older than 18 years with the desire to participate were enrolled in this study. For depression evaluation, we used the Hamilton Depression Rating Scale and for determination of percentage of NK cells in peripheral blood, flow cytometry method was used. **Results:** Our results showed that in patients with major depressive disorder, numbers of circulating NK cells have significantly reduced. **Conclusion:** According to our findings, depression is associated with “immune suppression”. NK cells are important in early phase of immunological surveillance versus viral infections and tumors. Indeed, depressive patients are susceptible to cancers and infections.

**Keywords:** major depressive disorder, natural killer cells

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### Introduction

Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities [1]. Psychosomatically, depression is a risk factor for many of the major medical illnesses such as heart disease, stroke, cancer and viral infections (e.g., HIV/AIDS) [2]. According to World Health Organization (WHO), by the year 2030 depression will cause disability than any other illness [3]. Psychoneuroimmunology is the study of the

interaction between psychological processes, the nervous and immune systems of the human body [4]. The brain and the immune system are the two major adaptive systems in the body that connect each other through signaling pathways [5]. Hence, mental factors such as depression have been shown to affect immune system function, likely through immunosuppression and immune activation [6]. Conversely, several lines of evidence suggest that immune system activation via infectious diseases, cancer, and autoimmune disorders is associated with the development of behavioural symptoms. The same mechanism has been also observed in the context of

chronic stress or major depression. These findings implicate a role of the immune system in behavioural disorders in a wide range of medical illnesses. Finally, a paradigm is proposed in which abnormal function either in the hypothalamic-pituitary-adrenal (HPA) axis or in the inflammatory response system disrupts feedback regulation of both neuroendocrine and immune systems and contributes to the development of neuropsychiatric and immunologic disorders [7].

Natural killer cells or NK cells are a type of cytotoxic lymphocyte which are critical for the innate immune system. The role of NK cells is analogous to that of cytotoxic T cells in the vertebrate adaptive immune response. NK cells provide rapid responses to viral-infected cells and prevent tumor formation, acting at around 3 days after infection [8]. NK cells are lymphocytes and major members of the innate lymphoid cell (ILC) family, which develop from CD34+ hematopoietic cells in the bone marrow and undergo terminal maturation in secondary lymphoid tissues [9]. In humans, NK cells are classically identified by the absence of the T cell receptor complex and presence of neural cell adhesion molecule (denoted CD56 according to the cluster designation [CD] system) [10]. The development of the antitumor/antivirus activities of NK cells is controlled by multiple mechanisms such as direct cytotoxic activity against target cells, antibody-dependent cell-mediated cytotoxicity, secretion of Th1-type cytokines, and interactions with dendritic cells [11]. So, in the present study we aimed to investigate the relationship of NK cells activity in patients with major depressive disorder.

## Methods

**Patients.** Patients older than 18 years with the desire to participate were enrolled in the study. After completing the written informed consent prior to the study, patients with no history of physical and mental disorders were included. The study population was selected in Sheikhorraes Clinic of Tabriz University of medical sciences between 2013 and 2014 after the diagnosis of major depressive disorder according to DSM-IV criteria by a psychiatrist. Patients Hamilton Depression Inventory was completed and peripheral blood NK-cells percentage was investigated in 35 patients with moderate depression. Control group are

35 normal individuals with the age of 18<years with no previous history of mental illness and the above mentioned process were conducted on this group too.

**Depression evaluation.** The Hamilton Depression Rating Scale, 17-item version was used by the therapist to assess the severity of depression in patients. For synchronization of severity of depression, patients with a score of 14-17 in the test group with moderate depression were selected.

**Percentage of NK cells in peripheral blood**  
From each patients with moderate depression and also the control group 5-10 ml of blood were collected and kept in EDTA tube. For determination of percentage of NK cells in peripheral blood, flow cytometry method was used in Shahid-Ghazi Hospital of Tabriz University of medical sciences. To determine the percentage of NK cells, anti-CD56 PE (Coulter Immunotech), in a BD FACS calibur flow cytometer were used. Control isotype was mouse IgG1 PE (IQ company, Netherland).

**Statistical analysis.** The data obtained from the study were analyzed with statistical software, SPSS-20. Normal data distribution was assessed by Kolmogorov-Smirnov test. P values less than 0.05 were considered statistically significant. For comparing between controls and patients, T-Test was used.

## Results

Statistical analysis showed that mean percentage of NK cells in patients (p) was  $15.97 \pm 6.82$  and in control group (c) were  $19.9 \pm 8.75$  (P value=0.04) (Figure 1 and 2).

## Discussion

In the present study, we recognized that in patients with major depressive disorder, numbers of circulating NK cells have reduced. For depression evaluation, we used the Hamilton Depression Rating Scale. For determination of NK cell percentage in peripheral blood, flow cytometry method was used.

Psychoneuroimmunological studies showed that stress and depression are associated with reduced proliferative responses of immune cells and impaired innate and adaptive immunity [12, 13]. In other words, depression is associated with “immune

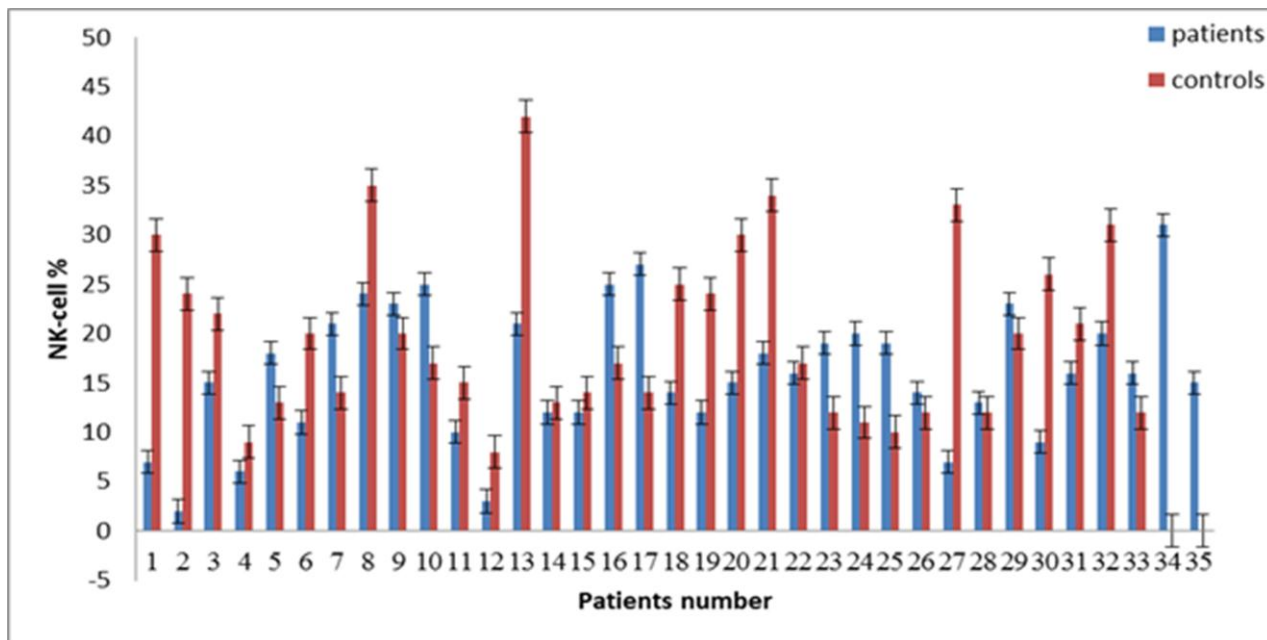


Figure 1. Comparative percentage of peripheral blood NK cells in depressive patients and healthy controls.

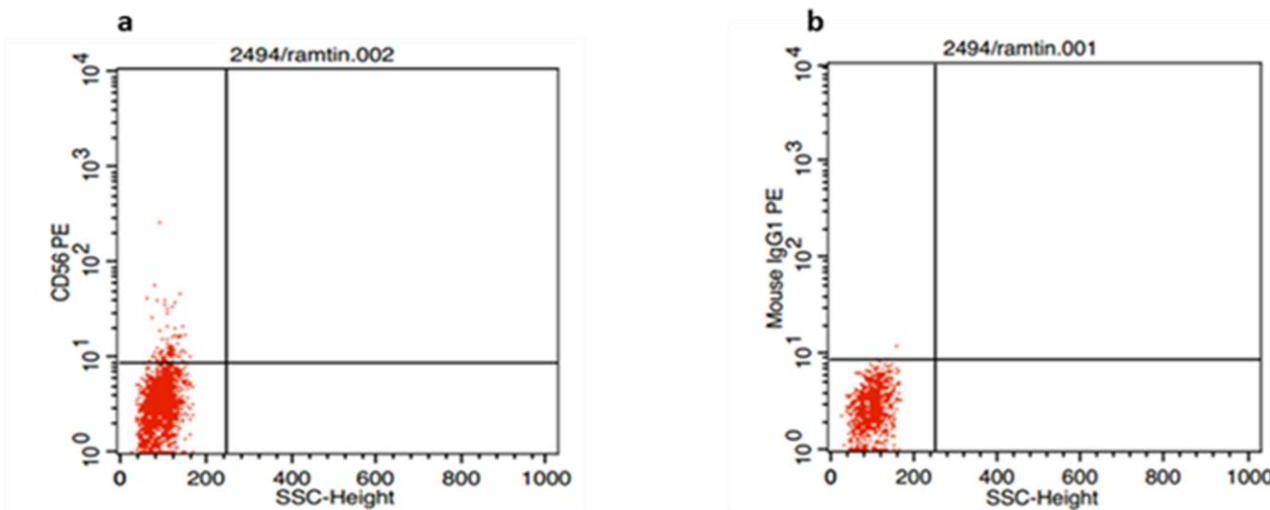


Figure 2. Flow cytometry plot of circulating NK-cells (anti CD56 PE, a) and related control (mouse IgG1 PE, b).

suppression”. Zorilla et al. showed that in depressed patients, NK cell cytotoxicity and lymphocyte proliferation are decreased [14]. There is some evidence about immune differences among the subtypes and species of major depression as defined in DSM-III and DSM-IV. Hypothalamic-pituitary axis (HPA) dysregulation may vary as a function of depression types. For example, a higher percentage of patients were diagnosed with major depression with psychotic features are dexamethasone nonsuppressors compared with patients meeting criteria for major depressive disorder without psychotic features [15,

16]. However, we synchronized the severity of patients in this study. Baniyash et al. showed that immune suppression is affected by the downregulation of the T cell receptor zeta chain, which is an important component of signal transduction in both NK cells and T cells [17]. In a follow-up of up to 19 years, 923 patients with some form of depression diagnosed in a psychiatry clinic showed a slightly elevated risk of developing cancer in comparison with the other members of a cohort of 143,574 persons who received prescriptions from a pharmacy [18]. However, it has become clear that NK

cells interact with various components of the immune system, and therefore have the potential to function as regulatory cells. While NK cells can assist in dendritic cell (DC) maturation and T-cell polarization, increasing evidence indicates that NK cells can also prevent and limit adaptive (auto) immune responses via killing of autologous myeloid and lymphoid cells [19]. Evans et al. has found that depressive symptoms are associated with decreased NK cell cytotoxicity in women with HIV [20]. Cruess et al. showed that enhancement of NK cell cytotoxicity are associated with the resolution of depressive symptoms [21]. Steven and his colleagues reported that in adults with major depression, the attenuation of circulating NK-cell with the increase in NK-cell activity may be due to the effect of compensation. However, further studies are warranted in this regard. It seems that the depression affects the NK-cell activity apart from its effect on the number of circulating NK-cell (CD56). Since there are some changes in the immune system of people with untreated or undiagnosed depression, the need for further treatment of mood disorders are required [22]. On the other hand, Farid et al. showed that there was no significant difference regarding NK cells between major depressed patients and healthy control subjects [23].

## Conclusion

We showed that circulatory numbers of NK cells have been diminished in patients with major depressive disorder. NK cells are important in early phase of immunological surveillance versus viral infections and tumors. Indeed, depressive patients are susceptible to cancers and infections. We suggest that the role of NK-cell in depressive patients should be evaluated through inhibitory and excitatory function of NK-cells in future studies.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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