

## Determination of vitamin B12, folate, and ferritin levels of inpatients in a psychiatry clinic: A one-year retrospective study

Bir psikiyatri kliniğinde yatan hastalarda B12 vitamini, folat ve ferritin düzeylerinin belirlenmesi: Bir yıllık retrospektif bir çalışma

Mehmet Hamdi Örum<sup>1</sup>, Mahmut Zabit Kara<sup>2</sup>, Oğuzhan Bekir Eğilmez<sup>1</sup>

<sup>1</sup>Department of Psychiatry, Adıyaman University Faculty of Medicine, Adıyaman, Turkey

<sup>2</sup>Department of Child and Adolescent Psychiatry, Adıyaman University Training and Research Hospital, Adıyaman, Turkey

### ABSTRACT

**Objectives:** This study aims to compare the vitamin B12, folate, and ferritin levels of inpatients in a psychiatry clinic.

**Materials and methods:** The study included 286 inpatients (178 males, 108 females; mean age 35.4±12.9 years; range, 15 to 76 years) treated in Adıyaman University Training and Research Hospital psychiatry clinic between 01 January 2017 and 31 December 2017. Patients' diagnoses and vitamin B12, folate, and ferritin levels were examined retrospectively.

**Results:** The most common diagnoses were schizophrenia (23.4%), bipolar affective disorder (23.1%), and major depressive disorder (11.5%). While there was no significant difference in vitamin B12 levels according to sex (p=0.850), folate level was significantly lower in males (p=0.001) and ferritin level was significantly lower in females (p=0.001). No difference was detected in the levels of vitamin B12, folate and ferritin in the comparison between diagnoses.

**Conclusion:** Deficiency in vitamin B12, folate, and ferritin levels may cause psychiatric symptoms. Due to the high number of patients with low vitamin B12 levels in our study, more attention may be paid to vitamin B12 replacement. Ferritin deficiency in females and folate deficiency in males are noteworthy. Further research are needed to identify more specific and detailed algorithms related to vitamin B12, folate, and ferritin to support the findings of this study and optimize the care given to patients suffering from psychiatric syndromes.

**Keywords:** Ferritin; folic acid; inpatients; psychiatry; retrospective study; vitamin B12.

### ÖZ

**Amaç:** Bu çalışmada bir psikiyatri kliniğinde yatan hastaların B12 vitamini, folat ve ferritin düzeyleri karşılaştırıldı.

**Gereç ve yöntemler:** Çalışmaya 01 Ocak 2017 ve 31 Aralık 2017 tarihleri arasında Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi psikiyatri servisinde yatarak tedavi gören 286 hasta (178 erkek, 108 kadın; ort. yaş 35.4±12.9 yıl; dağılım, 15-76 yıl) dahil edildi. Hastaların tanıları ve B12 vitamini, folat ve ferritin düzeyleri retrospektif olarak incelendi.

**Bulgular:** En sık görülen tanılar şizofreni (%23.4), bipolar affektif bozukluk (%23.1) ve majör depresif bozukluk (%11.5) idi. Cinsiyete göre B12 vitamini düzeylerinde anlamlı farklılık yokken (p=0.850) erkeklerde folat düzeyi (p=0.001) ve kadınlarda ferritin düzeyi (p=0.001) anlamlı olarak düşük idi. Tanılar arasındaki karşılaştırmada; B12 vitamini, folat ve ferritin düzeyleri arasında farklılık tespit edilmedi.

**Sonuç:** B12 vitamini, folat ve ferritin düzeylerinde eksiklik psikiyatrik semptomlara neden olabilir. Çalışmamızda B12 vitamini düzeyi düşük olan hasta sayısının fazla olmasına bağlı olarak B12 vitamini replasmanında daha dikkatli olunabilir. Kadınlardaki ferritin eksikliği ve erkeklerdeki folat eksikliği dikkat çekicidir. Bu çalışmanın bulgularını desteklemek ve psikiyatrik sendromu olan hastalara verilen bakımın optimize edilmesi için B12 vitamini, folat ve ferritinle ilişkin daha spesifik ve ayrıntılı algoritmaları belirlemek amacıyla ileri araştırmalar gerekmektedir.

**Anahtar sözcükler:** Ferritin; folik asit; yatan hastalar; psikiyatri; retrospektif çalışma; B12 vitamini.

Vitamins and minerals might influence mental health.<sup>[1-3]</sup> Deficiencies of specific vitamins and minerals produce consistent symptoms

of psychiatric disorder.<sup>[4]</sup> Thiamine deficiency, which is common in alcoholism, can produce confusion and psychotic symptoms, in addition

**Received:** April 17, 2018 **Accepted:** May 15, 2018

**Correspondence:** Mehmet Hamdi Örum, MD, Adıyaman Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı, 02100 Adıyaman, Turkey.  
Tel: +90 416 - 216 10 15 / 1186 e-mail: mhorum@hotmail.com

to neurological signs. Thiamine has been used successfully to treat patients with anxiety disorders.<sup>[5]</sup> Vitamin B6 has been used successfully for depression.<sup>[6]</sup> Niacinamide was found to suppress hypnotic and anticonvulsant activity, influence spinal cord activity, produce muscle relaxation and have aggression-diminishing effects.<sup>[7]</sup> The studies showed an association of depression status and severity with decreased serum vitamin D.<sup>[8,9]</sup> Dietary deficiencies of magnesium, coupled with excess calcium and stress may cause many cases of other related symptoms including hallucinations, agitation, anxiety, irritability, confusion, sleeplessness, headache and delirium.<sup>[10]</sup> The result of a study has suggested that alterations in essential trace elements manganese, copper and iron may play a role in the pathogenesis of schizophrenia.<sup>[11]</sup> Vitamin B12, folate and ferritin deficiency may also present with psychiatric symptoms.<sup>[12-14]</sup>

Vitamin B12 is a water-soluble essential vitamin and it is required for the hematopoiesis process, maintenance of nervous system functions, persistence of the gastrointestinal mucosa and continuation of other vitamin B12-dependent metabolic processes.<sup>[15,16]</sup> In addition, vitamin B12 is essential for central nervous system functions and regulates the mood of the person through various mechanisms. Neuropsychiatric disorders such as depressive disorders, cognitive and affective disorders, mental confusion, fatigue, delirium and paranoid psychosis can occur when B12 levels are deficient. Many researchers have described the lack of vitamin B12 in the pathogenesis of these processes.<sup>[17-21]</sup> Neurological findings, however, may not be specific enough to point directly to the deficiency of vitamin B12, for example, they may often manifest themselves as pallor.<sup>[22]</sup> The pathophysiology of the neurological and psychiatric manifestations of vitamin B12 deficiency is unclear.<sup>[21]</sup>

Folic acid is a member of the water-soluble vitamin B12 group and folic acid and its derivatives are generally called folate. Foliates are involved in the realization and regulation of many neurological events, such as cell proliferation, DNA synthesis and regulation, cell growth, DNA damage repair, monoamine synthesis, and synthesis of transmitters in the central nervous system. It is also used as a methyl source in cytosine methylation in epigenetic regimens.<sup>[23]</sup>

Many studies have found an association between depression and folate deficiency. Serum folate levels are found to be low in 10-30% of depressed patients.<sup>[24-26]</sup> There is also a link between folate deficiency and alcohol dependency. It has been suggested that folate deficiency may be due to inadequate nutritional deficiency and absorption in chronic alcoholics, or to accelerate folate metabolism of alcohol.<sup>[27]</sup> Iron-related disorders can also lead to psychiatric conditions resulting in mood changes. Ferritin is the main iron storage compound in the body and is present mainly in the reticuloendothelial cells of the spleen, liver and bone marrow. The mean concentration in men is twice that in women suggesting that the serum level reflects total body stores.<sup>[28-30]</sup>

A lot of studies have been done to investigate the association of vitamin B12, folate and ferritin with psychiatric disorders. Some of these studies have examined the relationship between psychiatric diseases and the mentioned parameters.<sup>[12,19]</sup> Significant results were found in some of the studies.<sup>[20,23]</sup> In some cases, there were non-significant differences within control groups.<sup>[31]</sup> Some of these studies were performed using patients who were followed while staying in the outpatient clinic<sup>[32]</sup> and others on inpatients.<sup>[33]</sup> Despite studies involving the association of different diseases with these parameters, studies comparing laboratory results of more than one psychiatric disorder in the same study are limited. The aim of this study is to examine the data such as age, sex, diagnosis, vitamin B12, folate, and ferritin levels of inpatients in Adiyaman University Training and Research Hospital Psychiatry Clinic. According to these results, we plan about the status of parameters evaluated in psychiatric inpatients to determine requirements and to carry out further researches.

## MATERIALS AND METHODS

### Study design and participants

A retrospective study was planned. The study was conducted by the researchers in accordance with the Helsinki Declaration. A total of 286 patients (178 males, 108 females; mean age 35.4±12.9 years; range, 15 to 76 years) who were hospitalized and treated in Adiyaman University Training and Research Hospital psychiatry clinic between 01.01.2017 and

31.12.2017 were included in the study. Patients whose vitamin B12, folate, and ferritin had been measured were screened through the hospital information system. The age and sex of patients diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition (DSM-5) criteria<sup>[34]</sup> were recorded and local ethics committee approval was obtained (Adiyaman University Ethics Committee Protocol Number: 2018/2-6).

### Blood analysis

All measurements were carried out in the Adiyaman University Training and Research Hospital Biochemistry Laboratory. Serum folate and vitamin B12 levels were measured using an immunoassay. Serum vitamin B12, folate and ferritin levels were determined using the UniCel® DxI 800 Immunoassay System-(Beckman Coulter, Inc., Brea, CA, USA) device. Periodic internal and external quality checks are carried out in the laboratory in order to determine possible errors that may affect the test data, as detailed previously. Biochemical data were evaluated based on the values of Adiyaman University Medical Faculty Central Biochemistry Laboratory. Folate deficiency was considered present when the serum folate level was less than 2.50 pg/mL (2.50-20.00 pg/mL), vitamin B12 deficiency was defined as a level less than 189 pg/mL (Normal: 189-833 pg/mL, Low: 0-100 pg/mL, Gray Zone-Uncertain:

100-200 pg/mL), and the ferritin level was accepted 11-306.8 ng/mL for females and 23.9-336.2 ng/mL for males.

### Statistical analysis

IBM SPSS for Windows version 22.0 program (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Independent t test was used to assess the mean differences between the two groups. In multiple groups, one way ANOVA (Bonferroni) test was used. Pearson correlation test was used to evaluate the relationship between the scales. Descriptive statistics and continuous variables were expressed as mean  $\pm$  standard deviation, while categorical variables were given as frequency and percentage. Post-hoc analysis was used. Statistical significance level was accepted as  $p < 0.05$  for all values.

## RESULTS

When analyzed according to sex, the average age was similar ( $p=0.855$ ). The statistics for diagnosis, patient quantities, male-female data and mean age were shown in Table 1. The most common diagnoses were schizophrenia (23.4%), bipolar affective disorder (23.1%) and major depressive disorder (11.5%), respectively. Schizophrenia, psychotic disorder, conversion disorder, cannabis use disorder, alcohol use disorder and opioid use disorder were mostly attributed to male patients (Table 1). In the

**Table 1.** Diagnosis distribution according to sex

Diagnosis	Sex				Total	Mean $\pm$ SD
	Male		Female			
	n	%	n	%		
Schizophrenia	51	76.1	16	23.9	67	37.3 $\pm$ 13.2
Bipolar affective disorder	33	50.0	33	50.0	66	37.5 $\pm$ 13.4
Schizoaffective disorder	5	41.7	7	58.3	12	35.5 $\pm$ 8.9
Psychotic disorder	10	71.4	4	28.6	14	26.9 $\pm$ 7.8
Major depressive disorder	16	48.5	17	51.5	33	40.6 $\pm$ 13.6
Anxiety disorder	15	50.0	15	50.0	30	33.3 $\pm$ 15.2
Obsessive compulsive disorder	2	25.0	6	75.0	8	37.4 $\pm$ 8.8
Conversion disorder	12	63.2	7	36.8	19	35.7 $\pm$ 11.2
Cannabis use disorder	10	90.9	1	9.1	11	24.5 $\pm$ 5.2
Alcohol use disorder	8	100.0	0	0.0	8	39.6 $\pm$ 7.8
Opioid use disorder	16	88.9	2	11.1	18	24.3 $\pm$ 4.9
<i>Total</i>	178	62.2	108	37.8	286	35.4 $\pm$ 12.9

SD: Standard deviation.

**Table 2.** Vitamin B12, folate and ferritin related data

Diagnosis	Vitamin B12		Folate		Ferritin	
	Mean±SD		Mean±SD		Mean±SD	
Schizophrenia	175.1±72.1		6.8±3.3		49.7±36.2	
Bipolar affective disorder	192.6±98.4		7.3±4.1		57.2±64.8	
Schizoaffective disorder	166.6±46.9		6.7±5.5		37.4±28.8	
Psychotic disorder	211.2±70.8		7.2±3.8		56.3±60.2	
Major depressive disorder	207.9±111.6		8.3±4.6		40.8±39.1	
Anxiety disorder	222.6±122.8		7.6±3.4		55.3±77.5	
Obsessive compulsive disorder	170.9±71.5		6.8±3.6		22.2±14.3	
Conversion disorder	182.3±113.8		6.7±2.8		42.5±41.8	
Cannabis use disorder	183.9±81.0		7.5±3.6		56.5±34.0	
Alcohol use disorder	179.5±47.8		7.9±2.7		73.7±67.9	
Opioid use disorder	238.9±170.1		5.9±2.9		46.6±19.5	
Total	194.2±100.1		7.2±3.7		50.3±51.1	
	Male	Female	Male	Female	Male	Female
	195.0±105.4	192.7±91.3	6.6±3.0	8.2±4.6	61.5±48.6	31.7±49.9
P value (between sexes)	0.850		0.001*		0.000*	

SD: Standard deviation; \* Significant difference.

obsessive compulsive disorder group, the majority consisted of females (Table 1). There were significant age-related differences within some diagnoses: schizophrenia-opioid use disorder ( $p=0.004$ ), bipolar affective disorder-opioid use disorder ( $p=0.003$ ), psychotic disorder-major depressive disorder ( $p=0.024$ ), major depressive disorder-marijuana use disorder ( $p=0.010$ ), major depressive disorder-opioid use disorder ( $p=0.000$ ). Details about the levels of vitamin B12, folate and ferritin are shown in Table 2. When the average of vitamin B12, folate and ferritin according to sex were examined; there was no significance in vitamin B12 ( $p=0.850$ ), folate was significantly lower in males ( $p=0.001$ ), and ferritin was found to be significantly lower in females ( $p=0.001$ ). Between diagnoses, in terms of average, vitamin B12 ( $p=0.328$ ), folate ( $p=0.738$ ), and ferritin ( $p=0.597$ ) levels were not significantly different. There were 189 patients (66.1%) with a vitamin B12 level  $<200$  pg/mL, 2 patients (0.7%) with a folate level  $<2.5$  pg/mL, and 58 patients (20.3%) with an abnormal ferritin level (normal level: 11-306.8 ng/mL for female and 23.9-336.2 ng/mL for male). In 69.1% of males and 61.1% of females, vitamin B12 level was below normal value ( $<200$  pg/mL) and there was no significant difference between sexes ( $p=0.166$ ). The percent of low ferritin was 33.3%

in females and 12.4% in males and there was a significant difference between them ( $p=0.001$ ). The rate of low ferritin was not significantly different between the diagnoses ( $p=0.495$ ). The rate of low vitamin B12 was not significantly different between the diagnoses ( $p=0.167$ ).

## DISCUSSION

Vitamins are dietary components which are necessary for life. They play a major role in health and their deficiency may be linked to symptoms of psychiatric disorders.<sup>[35]</sup> Studies on depression have shown that low folate and vitamin B12 serum levels seem to be associated with depression in the aged.<sup>[36,37]</sup> Systemic folate deficiency has been associated with macrocytic anemia and neuropsychiatric phenotypes. In some of these, despite normal systemic levels, folate transport to the brain is impaired in the so-called cerebral folate deficiency syndromes presenting as developmental and psychiatric disorders.<sup>[38,39]</sup> A result of a meta-analysis suggested that treatment with folate and vitamin B12 does not decrease the severity of depressive symptoms over a short period of time, but may be helpful in the long-term management of special populations.<sup>[40]</sup> On the other hand, some studies have reached different results. For instance, according to a study by

Sengul et al.,<sup>[41]</sup> supplementation of folic acid and vitamin B12 for postmenopausal women does not seem to be an effective intervention to reduce depressive symptoms. Although long term folic acid supplementation was well tolerated, with high levels of adherence, there was no evidence that it reduced the incidence of mood disorder compared to those taking placebo.

Esnafoglu and Yaman<sup>[42]</sup> investigated whether vitamin B12 and folic acid play a role in the aetiology of paediatric obsessive compulsive disorder. They have found significantly lower levels of vitamin B12 in the patient group compared to control group, whereas there was no significant difference between groups in terms of folate levels. They demonstrated that one carbon metabolism can play a role in the aetiology of obsessive compulsive disorder. Findings of Turksoy et al.'s<sup>[43]</sup> study suggested that some obsessive compulsive disorder patients might have vitamin B12 deficiency and higher homocysteine levels. The possibility that the vitamin B12 deficiency could be the consequence rather than the cause of obsessive compulsive disorder was suggested. The data suggested that iron deficiency may be associated with more severe tics with higher impact on Tourette syndrome children, independent of the presence of obsessive compulsive disorder or anxiety. Iron supplementation showed a trend towards improvement of tic severity upon follow-up.<sup>[44]</sup>

Studies involving the association of schizophrenia with vitamin B12, folate and ferritin are contradictory. The results of a study suggested that serum folic acid and vitamin B12 values in schizophrenia, bipolar disorder, and major depressive disorder did not differ from healthy controls.<sup>[45-47]</sup> Kemperman et al.<sup>[48]</sup> found that patients with schizophrenia had a lower level of vitamin B12 than healthy subjects, but that there was no difference between folate and vitamin B6. In a small double blind placebo-control study, Godfrey et al.,<sup>[49]</sup> showed symptom and social recovery in 17 schizophrenia patients with baseline low folate levels who received daily methylfolate supplementation (15 mg/day) for six months in addition to standard pharmacologic treatment. Levine and colleagues<sup>[50]</sup> demonstrated symptom improvement in schizophrenic patients supplemented with folic acid (2 mg/day), vitamin B6 (25 mg/day) and vitamin

B12 (400 mcg/day) in addition to regular antipsychotic treatment. According to Firth's<sup>[51]</sup> study, there is preliminary evidence that certain vitamin and mineral supplements may reduce psychiatric symptoms in some people with schizophrenia. Supplementation with both folate and vitamin B12 can be beneficial, especially in improving negative symptoms.<sup>[50,52]</sup> Vitamin and mineral supplements can be important in cases of substance and alcohol abuse.<sup>[53,54]</sup> The results of the studies suggested that some drug treatments might lead to a decrease in folic acid levels. In schizophrenic patients, serum folic acid levels were significantly reduced after typical antipsychotic treatment compared to those in pre-treatment and to those of the controls while they did not change after atypical antipsychotic treatment.<sup>[45]</sup>

In our study, the relationship between vitamin B12, folate and ferritin levels and some variables in men and women with various diagnoses was reported. Our work is primarily based on patients who have been hospitalized for a year in a psychiatric inpatient unit that serves an entire province. With this study, we used the age, sex and the diagnoses of all inpatient psychiatric patients within one year period. We can see sex predominance according to diagnosis. Male predominance in the group admitted due to substance use is significant and consistent with the literature.<sup>[55]</sup> In addition, this study is valuable because it allows the comparison of vitamin B12, folate and ferritin levels of multiple psychiatric disorders. Because comparing the results of different studies may not lead to accurate results due to differences in methods. Yet another important feature of our work is that it allows us to compare parameters that are evaluated according to age and sex. In the study, folate levels in males and ferritin levels in females were found to be significantly different. This may be due to hormonal differences, dietary characteristics, menstrual period and so on. In general, vitamin B12 levels in all ages, sexes and diagnoses are found to be low or near low. While some of the past studies have shown that vitamin and mineral replications are beneficial, some studies have indicated that they do not make a meaningful difference. To understand this, studies with fewer constraints are needed. When the results are evaluated together with the literature,

it was determined that further studies are needed to confirm the effects of vitamin B12, folate and ferritin on psychiatric disorders.

### Limitations

Major limitation of this study is its retrospective design. A prospective design starting from early periods of psychiatric disorder with regular follow-up scale evaluations would yield more convincing results about the nature of vitamin and mineral-psychiatric disorder interaction. Another major limitation of this study is its poor sociodemographic and scale content. Working with a larger number of patients and establishing a control group can lead to healthier results.

### Conclusion

As a result, these are just a few examples of how micronutrients can play a beneficial role in the treatment of several psychiatric illnesses. We think that the examination of vitamin and mineral levels of patients may be important in their follow-up. Further studies are needed to clarify this subject.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The authors received no financial support for the research and/or authorship of this article.

## REFERENCES

- Kaplan BJ, Crawford SG, Field CJ, Simpson JS. Vitamins, minerals, and mood. *Psychol Bull* 2007;133:747-60.
- Cornish S, Mehl-Madrona L. The role of vitamins and minerals in psychiatry. *Integr Med Insights* 2008;3:33-42.
- Davison KM, Kaplan BJ. Nutrient intakes are correlated with overall psychiatric functioning in adults with mood disorders. *Can J Psychiatry* 2012;57:85-92.
- Popper CW. Do vitamins or minerals (apart from lithium) have mood-stabilizing effects? *J Clin Psychiatry* 2001;62:933-5.
- Lonsdale D, Shamberger RJ. Red cell transketolase as an indicator of nutritional deficiency. *Am J Clin Nutr* 1980;33:205-11.
- Leeton J. Depression induced by oral contraception and the role of vitamin B6 in its management. *Aust N Z J Psychiatry* 1974;8:85-8.
- Bouwer C, Stein DJ. Hyperresponsivity to nicotinic acid challenge in generalized social phobia: a pilot study. *Eur Neuropsychopharmacol* 1998;8:311-3.
- Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry* 2008;65:508-12.
- Lee DM, Tajar A, O'Neill TW, O'Connor DB, Bartfai G, Boonen S, et al. Lower vitamin D levels are associated with depression among community-dwelling European men. *J Psychopharmacol* 2011;25:1320-8.
- Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses* 2006;67:362-70.
- Yanik M, Kocyigit A, Tutkun H, Vural H, Herken H. Plasma manganese, selenium, zinc, copper, and iron concentrations in patients with schizophrenia. *Biol Trace Elem Res* 2004;98:109-17.
- Lerner V, Kanevsky M, Dwolatzky T, Rouach T, Kamin R, Miodownik C. Vitamin B12 and folate serum levels in newly admitted psychiatric patients. *Clin Nutr* 2006;25:60-7.
- Coppen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. *J Psychopharmacol* 2005;19:59-65.
- Mills NT, Maier R, Whitfield JB, Wright MJ, Colodro-Conde L, Byrne EM, et al. Investigating the relationship between iron and depression. *J Psychiatr Res* 2017;94:148-55.
- Kozyraki R, Cases O. Vitamin B12 absorption: mammalian physiology and acquired and inherited disorders. *Biochimie* 2013;95:1002-7.
- Selhub J, Morris MS, Jacques PF, Rosenberg IH. Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. *Am J Clin Nutr* 2009;89:702-6.
- Bodnar LM, Wisner KL. Nutrition and depression: implications for improving mental health among childbearing-aged women. *Biol Psychiatry* 2005;58:679-85.
- Lerner V, Kanevsky M, Dwolatzky T, Rouach T, Kamin R, Miodownik C. Vitamin B12 and folate serum levels in newly admitted psychiatric patients. *Clin Nutr* 2006;25:60-7.
- Bottiglieri T. Homocysteine and folate metabolism in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;29:1103-12.
- Bottiglieri T, Laundry M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. *J Neurol Neurosurg Psychiatry* 2000;69:228-32.
- Herrmann W, Lorenzl S, Obeid R. Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders--current evidence and preliminary recommendations. *Fortschr Neurol Psychiatr* 2007;75:515-27. [Abstract]

22. Baytan B, Özdemir Ö, Erdemir G, Güneş AM. Çocukluk çağında vitamin B12 eksikliği klinik bulgular ve tedavi. *Uludağ Üniversitesi Tıp Fakültesi Dergisi* 2007;33:61-4.
23. Reynolds EH, Carney MW, Toone BK. Methylation and mood. *Lancet* 1984;2:196-8.
24. Wesson VA, Levitt AJ, Joffe RT. Change in folate status with antidepressant treatment. *Psychiatry Res* 1994;53:313-22.
25. Bender A, Hagan KE, Kingston N. The association of folate and depression: A meta-analysis. *J Psychiatry Res* 2017;95:9-18.
26. Abou-Saleh MT, Coppen A. Folic acid and the treatment of depression. *J Psychosom Res* 2006;61:285-7.
27. Hoyumpa AM. Mechanisms of vitamin deficiencies in alcoholism. *Alcohol Clin Exp Res* 1986;10:573-81.
28. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA* 1997;277:973-6.
29. Beard JL, Connor JR, Jones BC. Iron in the brain. *Nutr Rev* 1993;51:157-70.
30. Jacobs A, Miller F, Worwood M, Beamish MR, Wardrop CA. Ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *Br Med J* 1972;4:206-8.
31. Vahdat Shariatpanaahi M, Vahdat Shariatpanaahi Z, Moshtaaghi M, Shahbaazi SH, Abadi A. The relationship between depression and serum ferritin level. *Eur J Clin Nutr* 2007;61:532-5.
32. Atadag Y, Aydin A, Kosker HD, Kaya D, Basak F. Relationship of Vitamin B12 with depression-anxiety disorders: Retrospective cohort study. *Arch Clin Exp Med.* 2017;2:6-8.
33. Kara IH, Celer HG, Yilmaz A, Deler MH, Hakan L, Baltaci D, et al. Determination of hemogram, folic acid and B12 vitamin levels of depression patients followed up in psychiatry outpatient clinic. *Euras J Fam Med* 2014;3:69-78.
34. Amerikan Psikiyatri Birliği, Ruhsal Bozuklukların Tanısal ve Sayısal El kitabı. 5. Baskı (DSM-5). Tanı Ölçütleri Başvuru El kitabından, Çeviri editörü: Köroğlu E. Ankara: Hekimler Yayın Birliği; 2014.
35. Mikkelsen K, Stojanovska L, Apostolopoulos V. The Effects of Vitamin B in Depression. *Curr Med Chem* 2016;23:4317-37.
36. Petridou ET, Kousoulis AA, Michelakos T, Papatoma P, Dessypris N, Papadopoulos FC, et al. Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. *Aging Ment Health* 2016;20:965-73.
37. Nguyen PH, Grajeda R, Melgar P, Marcinkevage J, DiGirolamo AM, Flores R, et al. Micronutrient supplementation may reduce symptoms of depression in Guatemalan women. *Arch Latinoam Nutr* 2009;59:278-86.
38. Gougeon L, Payette H, Morais JA, Gaudreau P, Shatenstein B, Gray-Donald K. Intakes of folate, vitamin B6 and B12 and risk of depression in community-dwelling older adults: the Quebec Longitudinal Study on Nutrition and Aging. *Eur J Clin Nutr* 2016;70:380-5.
39. Ramaekers VT, Sequeira JM, Quadros EV. The basis for folinic acid treatment in neuro-psychiatric disorders. *Biochimie* 2016;126:79-90.
40. Almeida OP, Ford AH, Flicker L. Systematic review and meta-analysis of randomized placebo-controlled trials of folate and vitamin B12 for depression. *Int Psychogeriatr* 2015;27:727-37.
41. Sengül O, Uygur D, Güleç M, Dilbaz B, Simsek EM, Göktolga U. The comparison of folate and vitamin B12 levels between depressive and nondepressive postmenopausal women. *Turk J Med Sci* 2014;44:611-5.
42. Esnafoğlu E, Yaman E. Vitamin B12, folic acid, homocysteine and vitamin D levels in children and adolescents with obsessive compulsive disorder. *Psychiatry Res* 2017;254:232-7.
43. Türksoy N, Bilici R, Yalçın A, Özdemir YÖ, Ornek I, Tufan AE, et al. Vitamin B12, folate, and homocysteine levels in patients with obsessive-compulsive disorder. *Neuropsychiatr Dis Treat* 2014;10:1671-5.
44. Ghosh D, Burkman E. Relationship of serum ferritin level and tic severity in children with Tourette syndrome. *Childs Nerv Syst* 2017;33:1373-8.
45. Özsoy S, İzgi HB, Eşel E, Turan T, Baştürk M, Sofoğlu S. Şizofreni, bipolar bozukluk ve major depresif bozukluk hastalarında farmakoterapinin vitamin B12 ve folik asit düzeylerine etkileri. *Klinik Psikofarmakoloji Bülteni* 2009;19:128-34.
46. Haidemenos A, Kontis D, Gazi A, Kallai E, Allin M, Lucia B. Plasma homocysteine, folate and B12 in chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:1289-96.
47. Saedisomeolia A, Djalali M, Moghadam AM, Ramezankhani O, Najmi L. Folate and vitamin B12 status in schizophrenic patients. *J Res Med Sci* 2011;16:437-41.
48. Kemperman RF, Veurink M, van der Wal T, Kneegting H, Bruggeman R, Fokkema MR, et al. Low essential fatty acid and B-vitamin status in a subgroup of patients with schizophrenia and its response to dietary supplementation. *Prostaglandins Leukot Essent Fatty Acids* 2006;74:75-85.
49. Godfrey PS, Toone BK, Carney MW, Flynn TG, Bottiglieri T, Laundry M, et al. Enhancement of recovery from psychiatric illness by methylfolate. *Lancet* 1990;336:392-5.
50. Levine J, Stahl Z, Sela BA, Ruderman V, Shumaico O, Babushkin I, Osher Y, et al. Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biol Psychiatry* 2006;60:265-9.
51. Firth J, Stubbs B, Sarris J, Rosenbaum S, Teasdale S, Berk M, et al. The effects of vitamin and mineral supplementation on symptoms of schizophrenia:

- a systematic review and meta-analysis. *Psychol Med* 2017;47:1515-27.
52. Roffman JL, Lamberti JS, Achtyes E, Macklin EA, Galendez GC, Raeke LH, et al. Randomized multicenter investigation of folate plus vitamin B12 supplementation in schizophrenia. *JAMA Psychiatry* 2013;70:481-9.
  53. el-Nakah A, Frank O, Louria DB, Quinones MA, Baker H. A vitamin profile of heroin addiction. *Am J Public Health* 1979;69:1058-60.
  54. Cylwik B, Chrostek L. Disturbances of folic acid and homocysteine metabolism in alcohol abuse. *Pol Merkur Lekarski* 2011;30:295-9. [Abstract]
  55. Orum MH, Kustepe A, Kara MZ, Dumlupinar E, Egilmez OB, Ozen ME, et al. Addiction profiles of patients with substance dependency living in Adiyaman province. *Med Science* 2018. Available from: <https://www.ejmanager.com/fulltextpdf.php?mno=283898>