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Nutritional Status in Patients with Major Depressive Disorders: A Pilot Study in Tabriz, Iran

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ABSTRACT

Introduction: This study was conducted to assess the nutritional status in Iranian major depressive disorder patients. We also determined the relationship between nutrients intake with depression severity.
Methods: Seventy major depressive patients were selected randomly from outpatient depressive subjects, referred to Razi Psychiatry Hospital in Tabriz, Iran in 2007. Dietary intakes were recorded and compared with dietary reference intakes (DRIs). Definition of the disease and its severity were according to DSM-IV-TR and Hamilton Depression Rating Scale, respectively. Nutritionist III program, Chi-square, correlation and *t*-test were used for data analyses. Demographic, clinical and laboratory data were analyzed using SPSS software for windows (version13.0).
Results: According to dietary analysis, 11.4% and 55% of patients had dietary protein and energy deficiency, respectively. 97.1% and 95.7% of patients had less folate and B_{12} intakes than recommended dietary allowances. The mean (Mean ± SD) for plasma folate and B_{12} was 5.18±6.11 ng/ml and 389.05±346.9 pg/ml, respectively. Low plasma folate and B_{12} was observed in 51.4% and 50.0 % of patients, respectively. There was no significant relationship between blood folate and B_{12} levels with depression severity. Similarly, nutrients intake had no effect on depression severity.
Conclusions: Low plasma concentrations and low dietary intakes of folate and B_{12} are common among Tabrizian depressive patients. It seems that nutritional intervention for increasing folate and vitamin B_{12} intake must be considered as health promotive and preventative program for patients suffering from depression disorders.
Keywords: Major depression, Nutritional status, Folate, Vitamin B_{12}, Iran

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Introduction

Unipolar major depression is the fourth most important cause of premature mortality and disability [1]. Low dietary intake of folate and vitamin B_{12} has been implicated as a risk factor for depression [2]. Folic acid and vitamin B_{12} are important for normal functioning of the nervous system. One central biochemical reaction that unifies

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folate and vitamin B_{12} metabolism is the methylation of homocysteine to methionine, catalyzed by methionine synthetase. Folate (5'-methyltetrahydrofolate) provides the methyl group for the conversion of methionine to S-adenosylmethionine, the major methyl donor for most methyltransferase reactions [3].

Studies on the association of folate deficiency with depression extend back to the mid 1960's [3]. The initial studies were conducted on epileptic patients and showed that anticonvulsant therapy, which led to low serum folate levels, resulted in a higher incidence of mental symptoms including depression and psychosis [3]. The first study of the incidence of folate deficiency in psychiatric patients was described in 1967 by Carney [4], who showed high incidence of folate deficiency occurs in patients with depression (29–30%), organic psychosis (24%), and schizophrenia (20%). In several studies, plasma folate and vitamin B_{12} levels in depressive patients have been assessed. Low folate and vitamin B_{12} levels have been reported in some of them [5-17]. Approximately 10-30% of depressed patients may have low plasma folate levels, which may be higher than the general population, so it is postulated that there is relevance between depression and folate and vitamin B_{12} [18]. Depressed patients have impaired one-carbon metabolism regulation [15, 19, 20].

In Iran, there are very limited studies on the assessment of nutritional status among patients suffering depression; so the present study was designed to assess the nutritional status, focusing on folate and vitamin B_{12} deficiency; in patients with major depressive disorder. Moreover, the relationship between dietary folate, vitamin B_{12} and other nutrients intake with plasma folate and vitamin B_{12} levels and depression severity were determined.

Materials and Methods

Participants

This cross-sectional was performed among seventy outpatients (54 females and 16 males) referred to Razi Psychiatry Hospital in Tabriz, Iran in 2007. DSM-IV-TR diagnosis criteria for depression and Hamilton test were applied to distinguish depression by psychiatrist Score greater than 20 with Hamilton test were selected randomly.

The inclusion criteria were age of > 18 yr, and new episode of depression. A new episode was defined as the first depressive episode in a period of at least six months pervious to the study. Patients with severe physical or psychological illness such as history of mania, drug or alcohol misuse, use of psychotropic medication and vitamin supplementation for at least 8 weeks prior to the study, depression caused by physical illness or medication, megaloblastic anemia and pregnant or lactating women were excluded.

The study was approved by the Ethical Committee of Tabriz University of Medical Sciences, and also the informed consent was obtained from the patients or their attendants.

Procedures

Fasting blood samples were collected at 8.00 - 9.00 am. Blood samples were centrifuged at 1500 rpm and plasma was isolated and stored at -80 °C until analysis. Plasma folate and vitamin B_{12} concentrations were measured using radio assay method [Simul-TRAC MP Biomedical USA kit]. Folate and vitamin B_{12} deficiencies were considered as plasma folate and vitamin B_{12} less than 3 ng/ml and 200 pg/ml, respectively [21, 22]. Depression severity was assessed by the 17-item Hamilton Depression Rating Scale [23]. Dietary intake was assessed using three 24 hours-recalls in three different days (two consecutive no weekend and one weekend day). Dietary assessment was conducted by a nutritionist through face to face interview. Height was recorded to the nearest 0.1 cm with a stadiometer and weight was measured to the nearest 0.1 kg with a Seca scale.

Body mass index (BMI) was computed as weight (kg) divided by height (m^2). According to the BMI, patients were divided

to underweight (BMI≤18.5), normal weight (18.5<BMI<25), overweight (25≤BMI<30), and obese (30≤BMI) groups. According to the age, patients were divided to three groups 18-30, 30-50, and 50 -70 yr.

Measures

A structured clinical interview for DSM-IV-TR was used for diagnosis of the major depressive disorder. Its scoring was done by using from the 17-item Hamilton Rating Scale. The scale consists of 17 questions. Each question has between 3-5 possible responses. A score of 0-7 is considered to be normal, scores of 20 or higher indicate moderately severe depression [23]. Both of diagnosis and scaling of major depressive disorder were done by a psychiatrist with interview.

Statistical analysis

Dietary data were analyzed by Nutritionist III software. Demographic, clinical and laboratory data were analyzed using SPSS software for windows (version13.0). Chi-square and *t*-test were used to compare variables. For quantitative values, data were expressed as mean ± standard deviation (SD). Correlations were assessed by Pearson coefficient. Statistical significance was set at $P<0.05$.

Results

Of the 70 depressed patients (male: 16, female: 54); 10% (7) were illiterate, 25.7 % (18) had elementary education, 45.7% (32) had secondary or high school education, and 18.6 % (13) had higher high school educations. The mean and standard deviation for age, body mass index (BMI), and Hamilton Depression Rating Scale score in studied subjects are presented in Table 1. According to BMI, 1 patient (1.43%), 25 patients (35.71%), and 12 patients (17.14%) were underweight, overweight and obese, respectively.

Mean± SD for plasma folate and vitamin B_{12} concentrations in different age and sex groups, are shown in Table 2.

Table 1: Mean and standard deviation of general characteristics in studied subjects

	Women (n=54)	**Men (n=16)**	**Total (n=70)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Age (yr)	35.04 (11.81)	33.56 (12.81)	34.70 (11.97)
Weight (kg)	67.84 (14.35)	73.53 (6.22)	69.14 (13.14)
Height (cm)	160.32 (5.92)*	174.41 (5.08)	163.54 (8.25)
Body Mass Index (kg/m²)	26.20 (4.80)	24.43 (2.83)	25.80 (4.48)
Hamilton depression rate	27.70 (4.51)	26.88 (6.18)	27.51 (4.91)

*. There was a significant difference between men and women's height ($P < 0.05$).

Mean level of plasma folate and vitamin B_{12} concentrations of patients suffering depression were 5.18 ± 6.11ng/ml and 389.05 ± 346.9 pg/ml, respectively. No significant differences were found in plasma folate and B_{12} levels between different age and sex groups.

Table 2: Mean and standard deviation of plasma folate and vitamin B_{12} in studied subjects, in different age, and sex groups

Variables		**Folate (ng/ml)**	**Vitamin B_{12}(pg/ml)**
		Mean (SD)	**Mean (SD)**
Age (yr)	18-30 (n=29)	4.31(4.73)	384.65 (311.27)
	31-50 (n=33)	6.63 (7.38)	399.29 (401.29)
	51-70 (n=8)	3.56 (4.24)	362.84 (247.29)
Sex	Female (n=54)	5.36 (6.37)	420.43 (374.42)
	Male (n=16)	4.57 (5.33)	283.15 (206.69)

In different age and sex groups, no significant differences were observed for plasma folate and vitamin B_{12} levels

Prevalence of folate and B_{12} deficiency in different age and sex groups are shown in Table 3. Totally, 36 patients (51.4%) had low plasma folate levels (≤ 3ng/ml). Low plasma vitamin B_{12} (≤ 200 pg/ml) was seen in half of the studied subjects (35 patients). There was no significant difference between prevalence of folate or vitamin B_{12} deficiency in different age and sex groups.

Results for dietary assessment are shown in Table 4. According to the RDA, deficiencies in folate and vitamin B_{12} intakes were seen in more than 90% of patients. About 11.4% and 55% of studied subjects had low dietary protein and energy intakes, respectively. The main source of daily energy intake among depressed patients was carbohydrate (60.7%). The remaining was obtained from protein (13.1%) and fat (26.2%).

Table 3: Distribution of folate and vitamin B_{12} status in patients with major depressive disorder, in different age, and sex groups

Variable	Groups	Folate (ng/ml)		Vitamin B_{12}(pg/ml)	
		Deficient n (%)	Normal n (%)	Deficient n(%)	Normal n (%)
Age (yr)	18-30 (n=29)	17(58.6)	12(41.4)	14(48.3)	15(51.7)
	31-50 (n=33)	13(39.4)	20(60.6)	18(54.5)	15(45.5)
	51-70 (n=8)	6(75)	2(25)	3(37.5)	5(62.5)
Sex	Male (n=16)	11(68.8)	5(31.3)	8(50)	8(50)
	Female (n=54)	25(46.3)	29(53.7)	27(50)	27(50)

Plasma folate and B_{12} deficiency were defined as: plasma folate and B_{12} less than 3 ng/ml, and 200 pg/ml, respectively.

Table 4: Mean and standard deviation of dietary intakes and distribution of nutrients deficiency in patients with major depressive disorder

Nutrient	Intake Mean(SD)	Deficiency(< RDA) n (%)	Normal(≥ RDA) n (%)
Carbohydrate (g)	318.6 (360.49)	-	-
Protein (g)	58.9 (22.84)	8 (11.4)	62 (88.6)
Fat (g)	55.86 (26.68)	-	-
Energy (kcal/day)	1808.5 (675.82)	38 (54.3)	32 (45.7)
B_1 (mg/day)	1.56 (0.91)	12 (17.1)	58 (82.9)
B_2 (mg/day)	13.20 (11.98)	25(35.7)	45 (64.3)
B_3 (mg/day)	15.77 (7.68)	16(22.9)	54 (77.1)
B_6 (mg/day)	1.48 (0.99)	23(32.9)	47 (67.1)
Folate (µg/day)	125.61± 182.16	65(92.9)	5 (7.1)
B_{12} (µg/day)	1.14 ± 0.87	64(91.4)	6 (8.6)

Table 5: Correlation (Pearson's coefficient) between plasma folate and vitaminB_{12} with dietary variables and Hamilton score in patients with major depressive disorder

Dietary intake	Plasma Folate	Plasma Vitamin B_{12}	Hamilton Depression Rate
Carbohydrate	0.152	-0.083	0.106
Protein	-0.043	-0.008	0.047
Fat	-0.149	0.000	0.109
Energy	-0.08	-0.063	0.089
Vitamin B_2	0.054	0.096	- 0.031
vitamin B_6	-0.057	0.005	0.102
Folate	0.238*	0.030	- 0.005
Vitamin B_{12}	0.076	0.075	0.098
Plasma Folate	-	0.09	-0.22
Plasma Vitamin B_{12}	0.05	-	-0.14

$P < 0.05$

Assessed correlations between dietary macronutrients and micronutrients with plasma folate, B12 and Hamilton score are shown in Table 5. There was a negative but not significant relationship between plasma folate and vitamin B_{12} with Hamilton Depression Rating Scale score (r=-0.22, r=-0.14, respectively). No association was found between dietary folate and B_{12} with Hamilton Depression Rating Scale. A positive linear relationship was observed between plasma folate and its dietary intake (r = 0.24, $P<0.05$). Other nutrients (vitamins B_2 and B_6) did not have any significant relation with plasma folate or B_{12}.

Discussion

To the best of our knowledge, this survey was the first one for assessment of nutritional status in patients with major depressive disorder in Iran. Results of the study showed that 51.4% of patients with major depressive disorder had low plasma folate levels (≤ 3 ng/ml) and 50.0% of them had low plasma vitamin B_{12} levels (≤ 200 pg/ml). In the present study, prevalence of hypofolatemia was higher than the other studies [10, 13, 16, 24, 25].

Fava et al. [10] showed that the prevalence of folate deficiency (defined as plasma folate less than 1.5 ng/ml) in depressive patients was low (2.0%), whereas borderline values (1.5–2.5 ng/ml) were more common (17.0%). Lee et al. in a study in China showed that no patient with major depressive disorder had low plasma folate [13]. In the mentioned study, four patients (3.4%) had low erythrocyte folate. Papakastas et al. [16] in a study on 52 patients with major depressive disorder reported that 26.9% and 10.9% of them had plasma folate and vitamin B_{12} deficiency, respectively. In this study, low plasma folate and vitamin B_{12}, were considered as: ≤ 2.5 ng/ml and ≤ 200 pg/ml, respectively. In a study on 121 depressive patients only two patients (1.65%) had serum folate≤ 3 ng/ml [17]. In our study low vitamin B_{12} levels (≤ 200 pg/ml) were reported in 14 patients (11.57%). In another study [14] 26.3% and 29.9 % of psychiatric patients had serum cobalamin and folate less than 223 pg/ml and 3.1 ng/ml, respectively. Similarly, the prevalence of low plasma folate and vitamin B_{12} has been reported less than our results [26, 27].

In the present study, patients' plasma folate was 5.18 ± 6.11 ng/ml which is lower than many other studies [12, 13, 15]. In the USA, mean serum folate in depressive patients has been reported as 10.4 ng/ml [15]. In Hong Kong mean serum folate in depressive patients has been shown 24.6 ± 10.0 ng/ml [13]. In a study on 30 depressive patients plasma folate was 6.4 ± 4.0 ng/ml [12].

It seems that low dietary intakes of folate and vitamin B_{12} are the most common causes of low plasma levels. High daily intake of leafy green vegetables, in addition to soybean, green tea, meat and animal liver, all of which are rich sources of folate and vitamin B_{12}, can restore body folate and B_{12} reservoirs [21, 22]. Many authors suggested poor appetite and inappropriate food intake as symptoms of depression, which could result in low levels of folate and vitamin B_{12} [25]. Depression may affect the quality and quantity of food in the diet and so decreases blood levels of nutrients [25]. In the present study, three days dietary intake of folate and vitamin B_{12} were significantly lower than recommended dietary allowances (RDA) ($P < 0.05$). More than 90% of patients had deficiency in dietary folate and vitamin B_{12} intake. Energy intake in 54% of patients was less than recommended daily allowances (Table 4). Furthermore according to Pearson's correlation coefficient, there was a significant association between plasma folate and dietary intake of folate (r = 0.28, $P <0.05$), while there was no relation between dietary intakes and plasma levels of folate and vitamin B_{12} with depression severity (Table 5).

About 1.3% and 5.4% of depressive patients had low dietary vitamin B_{12} and folate intake [27]. In our study, lower prevalence of vitamin B_{12} and folate deficiencies might be related to high intake of meat and dairy products in Finnish diet [28]. Further-

more, they suggested that low dietary folate intake was related to three-fold increase in depression risk, but there was no relation between vitamin B_{12} and depression incidence [28]. There was a significant relation between folate intake and depression signs while there was no relation between vitamin B_{12}, B_6 or riboflavin and depression [27]. Miyake et al. in 121 outpatients with postpartum depression showed that mean intakes of folate and vitamin B_{12}, were 286.1 and 5.7 μg/day, respectively. In this study, there was no association between intakes of folate, vitamin B_{12}, or pyridoxine and the risk of depression [29]. In another study, there was no significant relationship between red cell folate with depression severity, measured by Montgomery Asberg Depression Rating Scale [30]. Likewise, plasma folate or vitamin B_{12} levels were not significantly related to depression [31]. Unlike these studies, Murakami et al. showed that higher dietary intake of folate was associated with a lower prevalence of depressive symptoms in Japanese men but not women [32]. In another study, dietary intakes of vitamin B_{12} and folate were related to depression [33]. In fact, it is not known whether the association between low levels of folate and depression is caused by a low intake, poor absorption or higher requirement of folate or whether it could be considered a result of poor appetite as a symptom of depression.

The main cause(s) for controversy among different studies results and between our study results with others could be due to geographical variations, racial and ethnic differences, genetic causes, different lifestyle, e.g. different cooking methods of vegetables, inadequate intake of B vitamins [34, 35] and not implementing fortification of grain products with folic acid.

Our study had some limitations. It was a cross sectional, descriptive study. We used only from one questionnaire for definition of major depression and not considered co morbid psychiatric diseases that may exist with major depression. It may have a selection bias in sampling. It was done only on depressive patients.

Conclusions

In general, comparison of the study's results with other studies shows higher prevalence of folate and vitamin B_{12} deficiencies in major depressive disorders patients. It seems that programs such as nutrition education, food fortification with folate and folate supplementation can increase these nutrients intake. Assessment of folate and B_{12} levels should be included in routine clinical assessment in depressed patients. Other indices of nutrient status (like blood cells folate and vitamin B_{12} concentrations) have not been measured, so further comprehensive epidemiological and clinical studies with higher sample size are required for assessment of these nutrients status and their relation to depression.

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References

[1] Murray O, Lopez AD. Global mortality, disability, and the contribution of risk factors. Global Burden of Disease Study. *Lancet* 1997; 349: 1436–1442.

[2] Sánchez-Villegas A, Doreste J, Schlatter J, Pla J, Bes-Rastrollo M, Martínez-González MA. Association between folate, vitamin B (6) and vitamin B (12) intake and depression in the SUN cohort study. *J Hum Nutr Diet* 2009; 22:122-33.

[3] Bottiglieri T. Hmocysteine and folate metabolism in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;

29: 1103-1112.

[4] Carney MW. Serum folate values in 423 psychiatric patients. *Br Med J* 1967; 4: 512–516.

[5] Abou-Saleh MT, Coppen A. Serum and red blood cell folate in depression. *Acta Psychiatr Scand* 1989; 80: 78 - 82.

[6] Alpert JE, Fava M. Nutrition and depression: the role of folate. *Nutr Rev* 1997; 55: 145-149.

[7] Carney MW, Chary TK, Laundy M, Bottiglieri T, Chanarin I, Reynolds EH, Toone B. Red cell folate concentrations in psychiatric patients. *J Affect Disord* 1990; 19: 207-213.

[8] Clement L, Boylan M, Miller GV, Rockwell M, Allred K. Serum levels of folate and cobalamin are lower in depressed than in nondepressed hemodialysis subjects. *J Ren Nutr* 2007; 17: 343–349.

[9] Dimopoulos N, Piperi C, Salonicioti A, Psarra V, Gazi F, Papadimitriou A, Lea RW, Kalofoutis A. Correlation of folate, vitamin B_{12} and homocysteine plasma levels with depression in an elderly Greek population. *Clin Biochem* 2007; 40: 604–608.

[10] Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. Folate, B_{12}, and homocysteine in major depressive disorder. *Am J of Psychiatr* 1997; 154: 426-428.

[11] Ghadirian AM, Ananth J, Engelsmann F. Folic acid deficiency and depression. *Psychosom* 1980; 21: 926-929.

[12] Ipcioglu OM, Ozcan O, Gultepea M, Ates A, Basoglu C, Cakir E. Reduced urinary excretion of homocysteine could be the reason of elevated plasma homocysteine in patients with psychiatric illnesses. *Clin Biochem* 2008; 41: 831–835.

[13] Lee S, Wing YK, Fong S. A controlled study of folate levels in Chinese inpatients with major depression in Hong Kong. *J Affect Disord* 1998; 49: 73-77.

[14] Lerner V, Kanevsky M, Dwolatzky T, Rouach T, Kamin R, Miodownik C. Vitamin B_{12} and folate serum levels in newly admitted psychiatric patients. *Clin Nutr* 2006; 25: 60-67.

[15] Morris MS, Fava M, Jacques PF, Selhub J, Rosenberg IH. Depression and folate status in the US population. *Psychother Psychosom* 1997; 72: 80-87.

[16] Papakastas GI, Petersen T, Mischoulon D, Ryan JL, Nierenberg AA, Bottiglieri T, Rosenbaum JF, Alpert JE, Fava M. Serum folate, vitamin B_{12} and homocysteine in major depressive disorder, part 1: predictors of clinical response in Fluoxetine – Resistant Depression. *J Clin Psychiatry* 2004; 65: 1090-1095.

[17] Wolfersdorf M, Konig F. Serum folic acid and vitamin B_{12} in depressed inpatients. A study of serum folic acid with radioimmunoassay in 121 depressed inpatients. *Psychiatr Prax* 1995; 22: 162-164.

[18] Mischoulon D, Burger JK, Spillmann MK, Worthington JJ, Fava M, Alpert JE. Anemia and macrocytosis in the prediction of serum folate and vitamin B_{12} status, and treatment outcome in major depression. *J Psychosom Res* 2000; 49: 183-187.

[19] Bottiglieri T, Hyland K. S-adnosylmethionine levels in psychiatric and neuro-logical disorders: a review. *Acta Neurol Scand Suppl* 1994; 154: 19-26.

[20] Papakastas GI, Alpert JE, Fava M. S-Adenosyl-methionine in the treatment of depression: a comprehensive review of the literature. *Curr Psychiatr Rep* 2003; 5: 460-466.

[21] Carmel C. Cobalamin (vitamin B_{12}). In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ (Eds.) Modern nutrition in health and disease. Baltimore: Lippincott Williams & Wilkins; 2006. pp. 482-497.

[22] Stopler T. Medical nutrition therapy foe anemia. In: Mahan LK, Escott-Stump S. (Eds.), Krause's Food & Nutrition Therapy. Canada: International Edition, Saunders, 2008; pp. 810-832.

[23] Akiskal HS. Mood Disorder. In: Sadock BJ and Sadock VA (Eds.), Kaplan and Sadock's Comprehensives Textbook of Psychiatry. New York: Lippincott Williams & Wil-

kins; 2005. pp. 1284-1297.

[24] Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation and monoamine metabolism in depression. *J Neurol Neurosurg Psychiatr* 2000; 69: 228-232.

[25] Hintikka J, Tolmunen T, Tanskanen A, Viinamäki H. High vitamin B_{12} level and good treatment outcome may be associated in major depressive disorder. *BMC Psychiatr* 2003; 3: 17.

[26] Pennix BWJH, Guralnik JM, Ferrucci L, Fried LP, Allen RH, Stabler SP. Vitamin B_{12} deficiency and depression in physically disabled older women: epidemiologic evidence from the women's health and aging study. *Am J Psychiatry* 2000; 157: 715 -721.

[27] Tolmunen T, Voutilainen S, Hintikka J, Rissanen T, Tanskanen A., Viinamaki H, Kaplan GA, Salonen JT. Dietary folate and depressive symptoms are associated in middle-aged Finnish men. *J Nutr* 2003; 133: 3233–3236.

[28] Tolmunen T, Hintikka J, Russunen A, Voutilainen S, Tanskanen A, Valkonin VP, Viinamäki H, Kaplan GA, Salonen JT. Dietary folate and the risk of depression in Finnish Middle-Aged men. *Psychother Psychosom* 2004; 73: 334-339.

[29] Miyake Y, Sasaki S, Tanaka K, Yokoyama T, Ohya Y, Fukushima W, Saito K, Ohfuji S, Kiyohara C, Hirota Y. Osaka Maternal and Child Health Study Group. Dietary folate, B_{12}, B_6 and B_2 intake and the risk of postpartum depression in Japan: The Osaka Maternal and Child health study. *J Affect Disord* 2006; 96: 133-138.

[30] Beaglehole B, Luty SE, Mulder RT, Kennedy MA, Joyce PR. Low red cell folate levels are associated with poor response to nortriptyline in major depression. *Acta Neuropsychiatrica* 2007; 19: 204-207.

[31] Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. Folate, vitamin B_{12}, homocysteine, and the MTHFR 677C-T polymorphism in anxiety and depression: The Hordaland Homocysteine Study. *Arch Gen Psychiatr* 2003;60: 618–626.

[32] Murakami K, Mizoue T, Sasaki S, Ohta M, Sato M, Matsushita Y, Mishima N. Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. *Nutr* 2008; 24:140-147.

[33] Sánchez-Villegas A, Henríquez P, Bes-Rastrollo M, Doreste J. Mediterranean diet and depression. *Public Health Nutr* 2006; 9: 1104-1109.

[34] Dawson DW, Waters HM. Malnutrition: folate and cobalamin deficiency. *Br J Biomed Sci* 1994; 51: 221-227.

[35] Golbahar J, Rezaian G, Bararpour H. Distribution of plasma total homocysteine concentrations in the healthy Iranians. *Clin Biochem* 2004; 37: 149-151.