Determination of folic acid and vitamin B12 serum levels in patients with major depressive disorder in Upper Egypt population: a case–control study

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Context
Major depressive disorder depression is classified as the third cause of morbidity in the world and is estimated to account for 12–15% of years on disability. The basis of this association may be that the synthesis of methionine requires a supply of both methyl groups from methyl-folate and also vitamin B12 as cofactor.

Aims
To estimate folic acid and vitamin B12 levels in patients diagnosed with major depressive disorder and their relation to the disease severity.

Settings and design
A case–control study involving patients diagnosed with major depressive disorder either first or recurrent episode was conducted.

Patients and methods
A total of 94 persons participated into this study, who were divided into 47 patients with major depressive disorder and 47 persons free of depression. Venous blood sample was taken from each patient and control for assessment of the folic acid and vitamin B12 serum levels.

Statistical analysis used
SPSS, version 23.0, was used for data management and data analysis. Mean ± SD, median, and range were used for descriptive statistics, and χ^2 test and Fisher's exact test for analytical.

Results
This case–control study uncovered that there is a significant correlation between vitamin B12 and folic acid levels and occurrence of major depressive disorder and insignificant correlation between vitamin B12 and folic acid levels and severity of depression or suicidal probability.

Conclusion
There is an inverse relation between vitamin B12 and folic acid serum levels and depression but no relation with the severity or suicide probability or disability degree.

Keywords:
depression, folic acid, vitamin B12

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Introduction

Major depressive disorder is classified as the third cause of morbidity in the world and is estimated to account for 12–15% of years on disability. It is estimated that, by year 2020, the increased burden of depression will lead to it being classified as the first cause of morbidity worldwide. Even though depression is predominantly expressed through psychological symptoms, it is manifested as a biochemical brain disturbance, and for that it is considered a biological disorder (especially major depression and bipolar disorder), and often responds well to biological treatments such as antidepressants [1].

Among 450 million people affected by mental health disorders, at any given moment, it is estimated that more than 150 million people experience depression in any period of their life, which means one every three people would experience depression and that one in 11 individuals will be affected at some time in their life by it [2].

Actually, an association between blood levels of vitamin B-complex and depression has been implied since the mid-1960s [3]. Many psychiatric disorders including major depression are widely linked to vitamin B12 deficiency [4].

Absorption, transfer, and metabolism aging-related disturbances as well as poor nutritional condition are all contributing factors [5].

Plausible biological mechanisms for the potential association between B-complex vitamins and depression have been demonstrated, focusing on their role in the methionine synthesis. The basis of this association may be that the synthesis of methionine requires a supply of both methyl groups from methyl-folate and also B12 vitamin as cofactor [6]. Methionine is in turn a precursor of S-adenosyl-methionine, the main methyl donor in many methylation reactions in the brain, including (a) one-carbon metabolism, which is directly relevant to the production of key monoamine neurotransmitters in the brain: dopamine, serotonin, and norepinephrine; (b) energy production and consumption by the brain tissue (thiamine); and (c) red blood cell formation and DNA synthesis [7–9].

Indeed, many studies have linked low folate levels or lower L-methyl-folate concentrations with major depressive disorders or lower L-methyl-folate concentrations [10,11].

Furthermore, more severe symptoms of depression and poorer response to therapy were founded in depressed patients with low folate level [12–14].

An increase in the effectiveness of antidepressants in late life may be induced by folate and, to a lesser extent, vitamin B12 [15–19], although evidence for the positive effects of vitamin supplementation on mood is still not convincing [20].

Patients and methods

A case–control study involving patients diagnosed with major depressive disorder either first or recurrent episodes were included. A total of 94 persons participated into this study, who were divided into 47 patients with major depressive disorder diagnosed according to DSM 5 diagnostic criteria[21] and 47 persons not complaining of depression matched for age and sex as a control group.

The study was approved and monitored by the Medical Ethics Committee, Assiut Faculty of Medicine (IRB#17101063).

Patients were assessed according to the Hamilton Rating Scale for Depression (HAM-D) and classified into mildly, moderately, severely, or very severely affected, and also control group was determined by HAM-D score between 0 and 7. Venous blood sample was taken from each patient and control after 8 h of fasting for assessment of the folic acid and vitamin B12 serum levels. Results were collected and correlated with the presence of depression, degree of severity of the disorder, and suicidal probability.

Methods

Psychiatric clinical interview for proper diagnosis of major depressive disorder included the following:

Full personal identification, complaints from patient and informant, history of present illness, past and family history, premorbid personality, and mental state examination and diagnosis of major depressive disorder is based on DSM 5 diagnostic criteria.

Hamilton depression rating scale scoring

A score of 0–7 is within the normal range (or in clinical remission).

A score of 8–13 is indicating mild depression.

A score of 14–18 indicating moderate depression.

A score 19–22 indicating severe depression.

A score of 23 or higher indicating very severe depression. The version used in this study is Hamilton's checklist of symptoms of depressive illness (HAM-D), and the Arabic version by Fateem [22,23].

The suicide probability scale was developed by John G. Cull and Wayne S. Gill (1990) to evaluate suicide probability and consists of 36 items for self-assessment (self-report). The scale scoring indicates that for males a score of 0–36 is below clinical, 37–44 mild, 45–51 moderate, and more than 52 is severe and also for females a score of 0–33 is below clinical, 34–38 mild, 39–43 moderate, and more than 44 is severe. The scale used in this study is the Arabic version 2003, which was translated and validated by Al Behairy [24].

Human vitamin B12 enzyme-linked immunosorbent assay kit

Commercially available enzyme-linked immunosorbent assay kit of SinoGeneClon Biotech Co. Ltd (No.28 Cangxin Road, YuHang District 311112, HangZhou, China), for the quantitative determination of human vitamin B12 concentrations was used according to manufacturer's instructions.

Human folic acid enzyme-linked immunosorbent assay kit

Commercially available enzyme-linked immunosorbent assay kit of SinoGeneClon Biotech Co. Ltd for the quantitative level of human folic acid in the sample was used according to manufacturer's instructions.

Statistical analysis

SPSS, version 23.0 (IBM, Corporate headquarters, 1 New Orchard Road, Armonk, New York 10504-1722, United States) was used for data management and data analysis. χ^2 test was used for comparing independent categorical variables. Fisher's exact test was used in the comparison of the groups. The Mann–Whitney *U* test was performed for the numerical variables not displaying normal distribution. The *P* value was set at 0.05, and all of the comparisons were two-tailed.

Results

Table 1 shows that number of cases in this study was 47 cases divided by Hamilton depression scale into mild cases (23.40% of cases), moderate (17.02% of cases), severe (31.92% of cases), and very severe (27.66% of cases). Table 2 shows that the mean age of patients with depression group was 38.32 ± 12.90 years and the mean age of the control group was 35.17 ± 9.52 years.

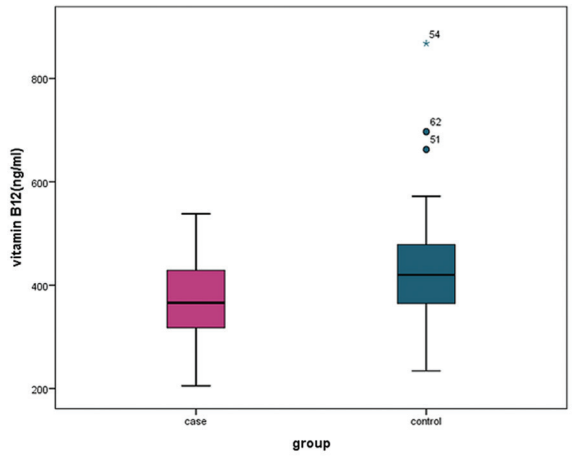
Regarding the sex distribution, the female and male percentages in the diseased group were 48.9 and 51.1%, respectively, whereas in the control group were 53.2 and 46.8%, respectively, with no statistical difference between any groups.

These relations were done by Mann–Whitney test. Table 3 shows that the patients with depression have significantly lower vitamin B12 serum levels than the control group. The mean ± SD level was 364.11 ± 87.23 ng/ml in the studied cases, whereas the level in control group was 433.21 ± 114.43 ng/ml (*P* = 0.005). Table 3 shows that the patients with depression have significantly lower folic acid serum levels than the control group. The level was 5.78 ± 1.61 and 8.28 ± 4.94 μg/l, respectively (*P* = 0.001).

These relations were done by Mann–Whitney test (Fig. 1 and 2).

Table 4 shows that there were a negative but not significant relation between HAM-D scale scores or suicidal probability scale scores and the levels of vitamin B12 and a positive but not significant relation between HAM-D scale scores or suicidal probability scale scores and folic acid. These relations were done by Spearman correlation coefficient (Fig. 3–6).

Figure 1



Box-and-Whisker plot showing vitamin B12 distribution among the two studied groups. This figure demonstrates the comparison between serum level of vitamin B12 measured in ng/ml in patients with major depressive disorder and control group, showing that the patients with depression have significantly lower vitamin B12 serum levels than the control group.

Table 1 Assessment of severity of major depressive disorder according to Hamilton depression scale

	Number of cases	%
Mild	11	23.40
Moderate	8	17.02
Severe	15	31.92
Very severe	13	27.66
Total	47	100

Table 2 Age and sex distribution of patients diagnosed with major depressive disorder in comparison with control

Items	Group		*P*
	Case (*n*=47)	Control (*n*=47)	
Age (years)			
Mean±SD	38.32±12.90	35.17±9.52	0.368
Median	36.00	34.00	
Range	19-70	19-65	
Sex [*n* (%)]			
Female	23 (48.9)	25 (53.2)	0.680
Male	24 (51.1)	22 (46.8)	

P<0.05.

Table 3 Serum level of vitamin B12 and folic acid in patients with major depressive disorder in comparison with control

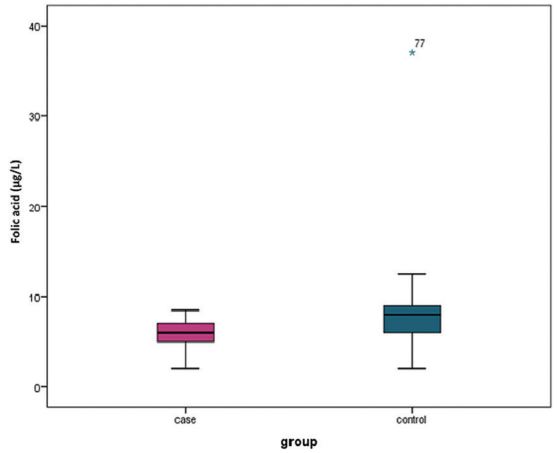
Items	Group		*P*
	Case (*n*=47)	Control (*n*=47)	
Vitamin B12 (ng/ml)			
Mean±SD	364.11±87.23	433.21±114.43	0.005
Median	366.00	420.00	
Range	205-538	234-868	
Folic acid (μg/l)			
Mean±SD	5.78±1.61	8.28±4.94	<0.001
Median	6.00	8.00	
Range	2-9	2-37	

P<0.05.

Table 4 Prognostic role of vitamin B12 and folic acid in the patient group

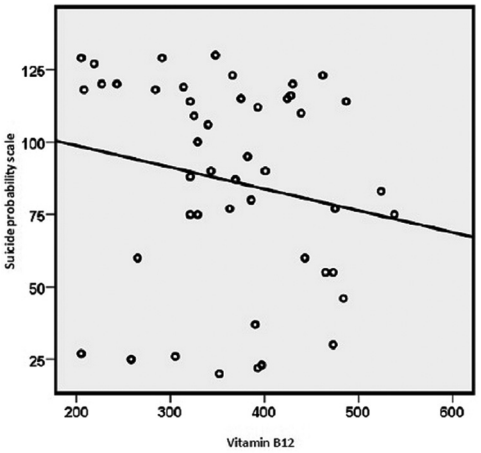
Items	Vitamin B12 (ng/ml)		Folic acid (μg/l)	
	r	*P*	*r*	*P*
Suicide probability scale	−0.264	0.073	0.218	0.142
Hamilton depression scale	−0.193	0.194	0.170	0.253

Figure 2



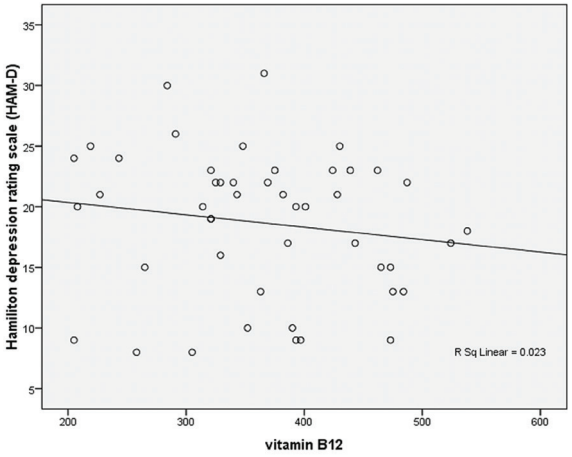
Box-and-Whisker plot showing folic acid distribution among the two studied groups. This figure demonstrates the comparison between serum level of folic acid in µg/ml in patients with major depressive disorder and control group, showing that the patients with depression have significantly lower folic acid serum levels than the control group.

Figure 3



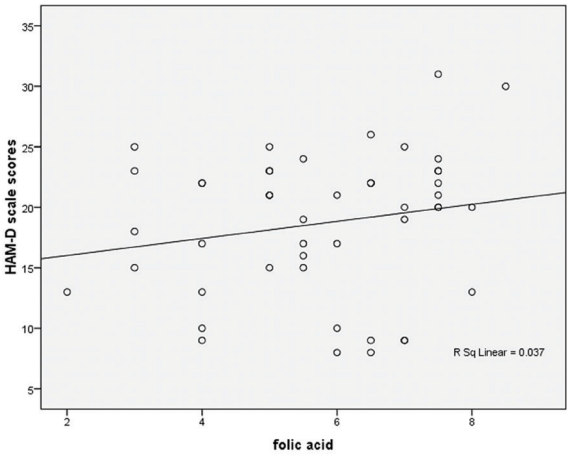
Scatterplot for suicidal probability scale with vitamin B12, indicating that there is a negative but nonsignificant relation between vitamin B12 levels and suicidal probability.

Figure 4



Scatterplot for HAM-D with vitamin B12, indicating that there is a negative but nonsignificant relation between vitamin B12 levels and severity of depression. HAM-D, Hamilton Rating Scale for Depression.

Figure 5



Scatterplot for HAM-D with folic acid, indicating that there is a positive but nonsignificant relation between folic acid levels and severity of depression. HAM-D, Hamilton Rating Scale for Depression.

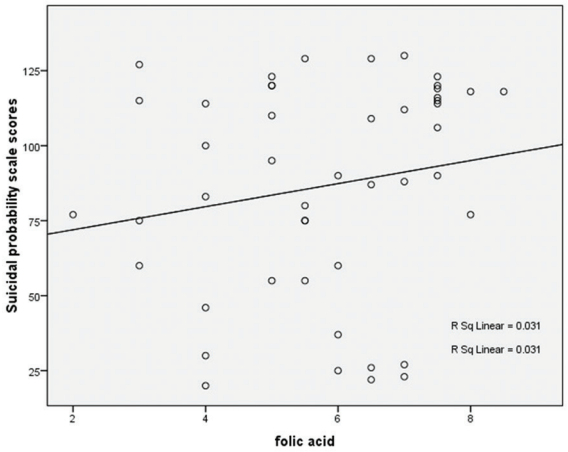
Discussion

The current work is a case–control study that comprises patients currently diagnosed with major depressive disorder either first or recurrent episodes. A total of 94 persons participated in this study, who were divided into 47 patients diagnosed with major depressive disorder and 47 of depression-free population as a control group. The applied scales in this study are HAM-D, Arabic version of Fateem[23] with 14 items, which divides the cases into mild (11 cases), moderate (eight cases), severe (15 cases), and very severe (13 cases), and suicide probability scale, the Arabic version 2003, which was translated and validated by Al Behairy [24]. Moreover, commercially available enzyme-linked immunosorbent assay kits of SinoGeneClon Biotech Co. Ltd were used for folic acid and vitamin B12 levels determination.

A significant difference between vitamin B12 levels in cases and control was found, with lower levels in depressed group. This finding is in agreement with Tiemeier *et al.* [11], who found that patients with vitamin B12 deficiency were nearly 70% more likely than the comparison patients to have a depressive disorder, and also with Gougeon *et al.* [25], who assumed that vitamin B12 may have a direct effect on the risk of depression.

Huang *et al.* [26], found that increased risk of depression is associated with high serum concentrations of vitamin B12. Similarly, Hintikka *et al.* [27], have supported their result that depression was positively correlated with vitamin B12 concentrations in 115 outpatients.

Figure 6



Scatterplot for suicidal probability scale with folic acid, indicating that there is a positive but nonsignificant relation between folic acid levels and suicidal probability scale scores.

This study revealed a significant difference between folate levels in cases and control, indicating that lower levels were found in depressed patients, whereas higher levels were found in control personnel, which is in agreement with Huang *et al.* [26], who speculated that depression associated with low level of folate. Similarly, serum folate concentrations were positively related to depression in reproductive age US women in 2011–2012 according to Nguyen *et al.* [28]. Folate concentrations were unrelated to depression in some studies as found the in studies of Watanabe *et al.* [29], and Gougeon *et al.* [25].

Depression is associated with neurotransmitters and hormone disturbances according to Miller [30], and Verma *et al.* [31]. Low levels of folate and vitamin B12 contribute to hyperhomocysteinemia, which correlates with the risk of depression according to Ng *et al.* [5].

There is no significant relation between vitamin B12 and folate deficiencies and severity of depression, which is in agreement with Elstgeest *et al.* [32], who observed no associations of vitamin B12 concentration and total homocysteine with severity of depressive symptoms.

We found no significant relation between vitamin B12 and degree of probability of suicide in major depressive patients.

No significant relation between folate deficiency and degree of probability of suicide in major depressive patients was reported in this study. This is in agreement with Wolfersdorf *et al.* [33], who compared nine suicides with matched controls, and had the result of no significant difference in erythrocyte or serum folate levels, and possibly, there is no relationship between suicidality and low folate.

Engström and Träskman-Bendz [34], found that the folate levels did not differ significantly between the diagnostic groups in their study, and the results of their study do not support the association between either low folate and major depression or between low folate and suicidality.

Conclusion

There is an inverse relation between vitamin B12 and folic acid levels and depression but no relation with the severity or probability of suicide.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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