LEVELS OF HOMOCYSTEINE, VITAMIN D, VITAMIN B12 AND FOLATE IN ADOLESCENTS WITH ANXIETY AND DEPRESSIVE DISORDERS

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Abstract

Background: Depression is the third leading cause of morbidity and mortality worldwide and expected to be the first one by 2030. Its relation to micronutrients is addressed sufficiently in adults. However, the studies in adolescence are scarce.

The aim of the work: assessing serum levels of vitamin B12, folate, homocysteine, and vitamin D levels in adolescents with depressive disorder.

Methodology: One hundred adolescents [12-18 years] with diagnosis of anxiety or depression were included in the study. Another 100 age and sex matched healthy children were included for comparison. Data were collected through detailed interviews for the adolescent and his/her family. The data collecting methods included the Children's Depression Inventory [CDI], and State-Trait Anxiety Inventory 1 and 2 [STAI-1 and STAI-2 anxiety scales] applied. Serum levels of vitamin B12, vitamin D, folate and homocysteine were measured.

Results: The patient group had significantly lower vitamin B12, folate and vitamin D levels when compared to healthy adolescents. Otherwise, homocysteine levels were significantly higher among patients than healthy adolescent groups. The CDI, STAI- I and II were inversely correlated with folate, vitamin B12 and vitamin D. but correlated positively with homocysteine was propitiate. Multiple linear regression analysis revealed that, folate, vitamin D, vitamin B12 and homocysteine remain significantly associated with disease severity [CDI]. However, only vitamin B12 was significantly associated with STAI-I and II. Others not significantly associated.

Conclusion: Vitamin B12, folate and vitamin-D deficiency with hyperhomocysteinemia were correlated with the development and severity of anxiety or depression. Vitamin B12 was the powerful contributing substance even after controlling for others.

Keywords: Hyperhomocysteinemia; Hypovitaminosis; Vitamin B12; Antidepressants; Anxiety

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INTRODUCTION

Depression and anxiety in adolescents are familial disorders that tend to recur frequently. Its prevalence is reported to be 0.4 – 8.3%. It is associated with a higher risk of suicide, substance use, negative life experiences, physical disease, and academic problems **[1,2].** However, the etiology is not fully explained. Thus, recognition of the etiopathogenesis in adolescent depressive disorders is important for the establishment of preventive and treatment strategies **[3].** This issue is complex due to heterogenous nature of depression, with multiple etiopathogenesis factors and the interaction between these factors **[4-6].**

In adults and old age subjects, the association between metabolic dysfunction and neuropsychiatric disorders are widely studies. The abnormalities in one-carbon metabolism are associated with or involvement in the pathogenesis of psychiatric disorders [e.g., bipolar disorder and schizophrenia **[7-9].** However, no sufficient studies in the childhood and adolescents.

Studies in adult populations provided significant association between adult depressive and bipolar disorders and reduced levels of vitamin B12, folate and hyperhomocysteinemia. These was supported by the significant reduction of antidepressants with folate and vitamin B12 supplementation for patients with folate deficiency **[10- 12].** Besides, vitamins D and E were suggested to play a critical protection role against somatic diseases [e.g., renal and hepatic diseases] through antioxidant mechanism. In addition, they have ani-inflammatory roles **[13, 14].**

In adolescents, it had been reported that, there is a significant reduction of depressive symptoms with dietary supplementation by multiple B-vitamins **[15,16].** The same effects were reported in psychosomatic diseases in different categories of population **[17-20].**

Different vitamins play an important role in the process of methylation reactions. These reactions are essential for the healthy brain and its function. In addition, the elevation of homocysteine lead to reduced synthesis of the catecholamine and other non-catecholamine neurotransmitters, which contribute to depression. Hyperhomocysteinemia is also associated with production of neurotoxic substances, which in turn affects the dopaminergic neurons. In addition, there are vascular endothelium and oxidative stress with increased homocysteine [a sensitive indicator of folate and vitamin B12 deficiency] and low vitamins E or D **[13,14, 21, 22].**

The studies dealing with this topic in adolescents are scarce. Thus, the current study was designed aiming to assess the serum levels of vitamin B12, folate, homocysteine, and vitamin D levels in adolescents with depressive disorder and if they play a possible role in the pathogenesis of adolescent depression.

METHODOLOGY

One hundred adolescents [12-18 years] were included in the study. In addition, another one hundred age and sex matched healthy children were included as a control group. All adolescents were selected from the outpatient clinics of Psychiatry and Pediatric departments [Faculty of Medicine, Al-Azhar University, Egypt]

Data were collected through detailed interviews for the adolescent and his/her family. The psychometric tests include an Arabic validated version of the Children's Depression Inventory [CDI], and State-Trait Anxiety Inventory 1 and 2 [STAI-1 and STAI-2 anxiety scales] applied. Written permission was obtained from each subject and their legal guardians. The study was reviewed and approved by the Institutional and Ethics Review Board of Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.

The diagnosis of depression in the study groups based on the DSM-5 criteria. The adolescents complete the questionnaires themselves [when possible] or with the help of psychiatric residents not included in the study.

Routine laboratory tests were performed side by side with vitamin B12, vitamin D, folate and homocysteine. Blood samples were collected in the morning after a night fasting and under sterile conditions.

Subjects on nutritional supplements in the previous year before the study, who had chronic systemic diseases, mental retardation, eating disorders, and any treatments interferes with the studied substances, were excluded.

The Children's depression inventory [CDI] was originated by M. Kovacs bearing in mind that "child depression exists, it can be observed and measured, its characteristics resemble adult depression". The inventory was validated in different countries. It comprised 27 items in total. The depression was confirmed if the score above 19. For each item, the child was asked to choose the most relevant option from 3 alternative describing his/her condition in the previous 2 weeks. The answer for each item was scored from 0 to 2 points. Thus, the highest total score is 54, and increased score indicate increased the disease severity **[23].**

State-trait anxiety inventory- I and II [STAI-I, STAI-II]: The questionnaire has two subdomains, each of which has 20 items: Situational and continuous Anxiety Scale. The Situational Anxiety Scale determines how a subject feels under specific circumstances at a specific time and it is scored by choosing either 'nothing', 'a little bit', 'a lot', or 'completely' to denote the severity of the feeling, thought, or behavior. The Continuous Anxiety Scale appraises how the subject feels irrespective of situations or circumstances. In addition, it contains direct or inverted statements. The total score for the two subscales changes between 20 and 80. A higher score indicates a higher level of anxiety. Anxiety diagnosed at scores higher than 45.

Vitamin B12, folate, homocysteine, and vitamin D determinations: One ml of venous blood sample was collected in tubes contain anticoagulant, centrifuges at 5000xg for 5 minutes at room temperature. Then, vitamin D [D2 and D3] were measured by the chemiluminescence microparticle immunoassay. Vitamin B12 [total cobalamin] was measured chemi-luminescence microparticle immunoassay intrinsic factor B12 assay using the commercial kits supplied by Abbott laboratory. Folate was measured by chemiluminescent microparticle Folate binding protein ARCHITECT Folate assay with commercial kits. Furthermore, homocysteine measured by chemiluminescent immunoassay method using kit supplied by Abbott Laboratory.

Data analysis: Statistical analysis was performed through introducing collected anonymized data to the SPSS 22.0 software computer package [IBM SPSS Statistics for Windows, Armonk, NY, USA]. Descriptive statistics included mean±SD [Standard deviation] for continuous normally distributed variables, and relative frequency and percentages for qualitative variables. The significant differences between means were assessed by the independent sample's "t" test. The significant association between two categorical variables were assessed by Chi Square test. Pearson correlation coefficient was calculated between continuous variables to investigate direct relationships. P value < 0.05 was accepted as the limit of significance.

RESULTS

There were no significant differences between the patient's and control groups regarding adolescent gender or age. The patient group had significantly lower vitamin B12, folate and vitamin D levels when compared to healthy adolescents. Otherwise, homocysteine levels were significantly higher among patients than healthy adolescent groups [Table 1].

The CDI, STAI- I and II were inversely correlated with folate, vitamin B12 and vitamin D. However, their correlation with homocysteine was propitiate [Table 2].

Running multiple linear regression analysis, folate, vitamin D, vitamin B12 and homocysteine remain significantly associated with disease severity [CDI]. However, only vitamin B12 was significantly associated with STAI-I and II. Others not significantly associated [Table 3].

Table [1]: Comparison between patients and healthy adolescents regarding studied variables

		Patient	Healthy	Test	p
Sex [n, %]	Male	36[36.0%]	34[34.0%]	0.09	0.76
	Female	64[64.0%]	66[66.0%]		
Age [year]	Mean±SD	15.22±1.02	14.93±1.53	2.48	0.11
	Min. – Max.	13-17	12-18		
CDI	Mean±SD	25.18±4.17	13.95±2.67	***22.66***	***<0.001****
	Min. – Max.	19-34	7-18		
STAT-1	Mean±SD	57.78±6.05	32.15±7.44	***21.50***	***<0.001****
	Min. – Max.	33-72	20-61		
STAT-2	Mean±SD	57.41±5.99	36.30±7.45	***22.07***	***<0.001****
	Min. – Max.	37-76	22-65		
Folate [ng/ml]	Mean±SD	5.39±1.92	5.83±0.97	***2.02***	***0.045****
	Min. – Max.	2.8 – 9.6	3.3 – 10.50		
Vitamin B12 [pg/ml]	Mean±SD	148.46±21.48	266.43±27.52	***33.78***	***<0.001****
	Min. – Max.	102-205	190-320		
Vitamin D [ng/ml]	Mean±SD	10.86±1.87	20.37±5.20	***17.20***	***<0.001****
	Min. – Max.	5.60-17.1	9.60-29.3		
Homocysteine [µmol/L]	Mean±SD	14.57±5.19	9.85±2.11	***8.42***	***<0.001****
	Min. – Max.	7.8-37.40	5.9-17.60		

Table [2]: Correlation between CDI and other variables in the study group

	CDI		STAI-1		STAI-2	
	r	*p*	*r*	*p*	*r*	*p*
Folate [ng/ml]	-0.188	*0.008**	-0.174	*0.014**	-0.166	**0.019***
Vitamin B12 [pg/ml]	-0.777	*<0.001**	-0.80	*<0.001**	-0.82	**<0.001***
Vitamin D [ng/ml]	-0.664	*<0.001**	-0.629	*<0.001**	-0.635	**<0.001***
Homocysteine [µmol/L]	0.420	*<0.001**	0.372	*<0.001**	0.387	**<0.001***

Table [3]: Multivariate linear regression analysis among studied populations

		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
CDI	Folate	-0.410	0.192	-0.095	-2.140	0.034*
	Vitamin D	-0.188	0.071	-0.175	-2.667	0.008*

	Vitamin B12	-0.061	0.007	-0.594	-8.873	<0.001*
	Homocysteine	0.126	0.072	0.088	1.758	0.080*
STAI-1	Folate	-0.549	0.348	-0.068	-1.578	0.116
	Vitamin D	-0.131	0.128	-0.065	-1.029	0.305
	Vitamin B12	-0.143	0.013	-0.738	-11.349	<0.001*
	Homocysteine	0.051	0.130	0.019	.389	0.698
STAI-II	Folate	-0.486	0.342	-0.059	-1.422	0.157
	Vitamin D	-0.112	0.126	-0.055	-.890	0.375
	Vitamin B12	-0.148	0.012	-0.757	-12.016	<0.001*
	Homocysteine	0.078	0.128	0.029	.611	0.542

DISCUSSION

The results of the current work indicated that, depression and anxiety were significantly associated with reduced folate levels, hypovitaminosis D and B12 and hyperhomocysteinemia. The correlation analysis confirmed this association. However, when multiple variables are considered, all still associated with CDI. But, only vitamin B12 was the only significant associate with STAT-1 and 2. Thus, all variables could play a role in pathogenesis of depression and its severity. However, only vitamin B12 continued to be significantly associated with anxiety. These results reflected that, vitamin B12 is the most important nutrient among studied variables. These results are in line with previous observational studies in children and adolescents, that indicated that, the severity of depression and anxiety symptoms significantly and negatively correlated with vitamin B12 and folates. The correlation with homocysteine was proportionately correlated

Several observational studies showed that the severity of anxiety and depression symptoms was negatively correlated with vitamin B12 and folate levels, and was positively correlated with homocysteine levels in children and adolescents **[24, 25].**

Vitamin B12 and folate deficiency induced depression and anxiety through increased levels of homocysteine. Vitamin B12 and folate are critical for the metabolism of homocysteine. The increased values of homocysteine exert its action through oxidative stress, mitochondrial dysfunction and increased apoptosis of dopaminergic neurons. Finally, induced depression or anxiety **[26, 27].**

In addition, vitamin B12 and folate deficiency associated with hyperhomocysteinemia played an immune modulatory role, with induction of persistent chronic inflammatory state. This in turn can dysregulate the function of the hypothalamic-pituitary-adrenal [HPA] axis, disturb metabolism of neurotransmitters, impair neuronal function and disturb neural activity of the brain areas regulating emotions and leads to anxiety and depression **[28-29].**

The results of **Tan et al. [27]** is partially in line with the current work. They found a negative correlation between vitamin B12 and severity of symptoms related to anxiety or depression. However, they reported no significant correlation was observed between folate, homocysteine and symptoms severity of anxiety and depression.

Previous studies tried to explain the potential pathophysiologic mechanism of how vitamin B12 & folate deficiency and hyperhomocysteinemia are associated with symptoms of depression or anxiety. **Trautmann et al. [30]** showed that vitamin B12 supplementation are associated with significant reduction of the DNA methylation of the Ntrk-2 3′UTR, with increased expression of Ntrk-2 [a gene of brain-derived neurotropic factor receptor, which plays an important role in etiopathogenesis of depression and response to the antidepressant drugs], especially in prefrontal cortex.

Budni et al. [31] also showed that, folate had antidepressant actions with the involvement of N-methyl-D-aspartate receptors and the L-arginine-nitric oxide [NO] pathway.

Halaris et al. [32] reported that, folate deficiency is associated with a significant reduction of neurotransmitters [serotonin, dopamine, and norepinephrine]. The reduction of neurotransmitters is associated with neurochemical deterioration and lead to depression.

Wang et al. [15] conducted a meta-analysis to investigate the association between diet quality and depressive symptoms in youth. They concluded that, their study provides a preliminary evidence for the association between depressive symptoms in youth and the diet quality, regardless the heterogenous nature of the included trials.

They elucidate the importance of nutrition interventions to reduce depressive symptoms in youth.

Russell-Jones [2022] reported that vitamin B12 deficiency associated with depression. The incidence of depression is higher among vegetarians due to insufficient vitamin-B12 intake. They added the measurement of serum vitamin B12 alone in such cases is not sufficient and homocysteine levels should be checked at the same time.

The current work is valuable as it addressed an area with insufficient research. As adolescence is associated with intensive brain remodeling, the value of our work increased and micronutrient supplementation in this period seems to be critical. However, it was beyond the scope of the current study. This representing a limiting step that needs to be explored in the future literature.

Conclusion: Vitamin B12, folate and vitamin-D deficiency with hyperhomocysteinemia were correlated with the development and severity of anxiety and/or depression. Among those nutrients, vitamin B12 was the powerful factor with a marked correlation with disorders even after controlling for other variables.

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