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Original Article

Folate Deficiency: Is it Related to the Development of Depression

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ABSTRACT

Objectives: To determine the frequency of serum folate deficiency among patients with depression and to compare mean serum folate levels with the severity level of depression.

Study Design: Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Mental Health, Rawalpindi Pakistan, from Sep 2021 to Feb 2022.

Methodology: We consecutively recruited 155 study subjects. Basic demographic data were recorded. The severity of depression was assessed using the Hamilton Depression Rating Scale–Urdu version (HAM-D U). Blood samples were collected to determine serum folate before commencing any treatment for depression; serum Folate levels were assessed at the Armed Forces Institute of Pathology.

Results: The mean HAM-D score was 17.14±4.29, with minimum and maximum scores of 8 and 22. 97(62.6%) cases had mild–moderate depression, and 58(37.4%) patients had severe depression. The mean serum folate levels were 3.10±1.40 ng/ml. There were 57(36.8%) cases that had normal folate levels, 45(29%) cases that had borderline folate levels, and 53(34.2%) cases that had folate deficiency. The frequency of borderline folate deficiency was statistically higher in cases with severe depression, (p-value<0.001).

Conclusion: Results of this study highlight that the frequency of borderline–folate deficiency was statistically higher in cases with moderate and severe depression.

Keywords: Depression, Folate, Hamilton depression rating Scale (HAM).

How to Cite This Article: *Bajwa AA, Ali S, Khan SA, Raza H, Hussain F, Nazir TB. Folate Deficiency: is it Related to the Development of Depression. Pak Armed Forces Med J 2023; 73(4) 989-992. DOI: https://doi.org/10.51253/pafmj.v73i4.9187*

INTRODUCTION

Depression is a multi-factorial disorder, with biological, psychological and social factors playing a role in its etiology.[1] Vitamins are essential in mood regulation, a necessary part of maintaining the correct balance of nutrients and vitamins in the diet.[2] Researchers have found that a reduced risk of developing depressive symptoms was associated with a healthy diet. A healthy diet has high nutrient levels of B vitamins, vitamin D, and folic acid, which are all involved directly in serotonin synthesis.[3] Therefore, an unhealthy diet has been considered a predisposing factor for depression based on vitamin deficiency, and a change in diet could directly affect mental health.[4]

It has been shown that a healthy diet containing all the nutrients, specifically folate protects, while its deficiency is associated with an increased risk of developing depression and relapses.[5] S-adenosyl-methionine (SAMe) is a metabolite of folate used to produce dopamine, norepinephrine, and serotonin neurotransmitters.[6] Therefore deficiency of folate leads to lower levels of these neurotransmitters, consequently providing a neurochemical diathesis for depression.[7] Studies conducted on patients with unipolar depression showed a significant reduction in scores on Beck Depression Inventory (BDI) after receiving folate.[8,9] On the contrary, studies emphasise that the relationship between serum folate and depression is there, but this relationship is inconclusive.[10]. The majority of the reported studies have been written on the Western population. Furthermore, there is a lack of literature investigating this relationship within the Pakistani people. Therefore, this study aims to study the relationship between serum folate and different severities of depression in a Pakistani sample so that risk stratification and management can be planned accordingly.

METHODOLOGY

After approval of the Ethical Review Committee (vide IERB No. 0021/20), the cross-sectional study was conducted at the Armed Forces Institute of Mental Health, Rawalpindi Pakistan, from September 2021 to February 2022. The sample size was estimated using

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Received: 21 Aug 2022; revision received: 08 Oct 2022; accepted: 11 Oct 2022

the WHO sample size calculator based on the anticipated population was 11.3%.[11]

Inclusion Criteria: All newly reporting patients of either gender, aged 18-50 years having clinical depression were diagnosed using ICD-10 criteria,[12] were included, and severity was assessed using the HAM-D scale.[13]

Exclusion Criteria: Patients taking any folic acid supplements in the last three months, patients with medical conditions that are associated with folic acid deficiency (including megaloblastic anaemia, hyperparathyroidism and Crohn's disease, celiac disease) and patients on medications that interfere with folic acid metabolism were excluded from the study.

To assess the severity of depression Hamilton Depression Rating Scale–Urdu version (HAM-D U) was used.[14] HAM-D scores severity of depression out of a total score of 5013. Although the HAM-D lists 21 items, the Scoring is based on the first seventeen. It generally takes 15-20 minutes to complete the interview and score the results. Nine items are scored from 0-2. Eight items are scored on a 5-point scale (0-4); nine items are scored as 0 absent 1–doubtful or trivial 2–present, eight items are scored as 0–absent 1–mild 2–moderate 3–severe 4 incapacitating. An overall sum of scores is calculated to obtain a Depression Severity Score out of 50. The HAM-D scores are categorized as follows 8-13 mild 14-18 moderate 19-22 severe equal to or greater than 23 very severe. The severity was categorized into two groups mild to moderate depression (score 0–18) was designated as Group-A while and severe depression (score>18) was designated as Group-B.

Before commencing any treatment for depression, blood samples were collected for serum folate levels to be assessed at the Armed Forces Institute of Pathology (AFIP). The generated reports were collected. Serum Folate levels above 4ng/ml were considered normal, 2-4 ng/ml borderline, while less than 2ng/ml was considered folate deficiency.[15] Individuals were categorized as having normal or deficient folate levels accordingly, and the readings were entered for data analysis. Depression severity scores (HAM-D score) and serum folate were recorded for all participants.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Independent sample t-test and Chi-square test were applied to explore the inferential statistics. The *p*-value of ≤0.05 was set as the cut-off value for significance.

RESULTS:

In the study, mean age of participants was 33.80±9.26 ranging between 18 and 50 years. The mean HAM-D score was 17.14±4.29, with minimum and maximum scores of 8 and 22. There were 97(62.6%) cases of mild–moderate depression and 58(37.4%) cases had severe depression. The mean serum folate levels were 3.10±1.40 ng/ml with minimum and maximum values of 1.0 and 5.54ng/ml. There were 57(36.8%) cases with normal folate deficiency, 45(29%) cases had borderline and 53(34.2%) cases had folate deficiency (Table-I).

Table-I Demographic Characteristics (n=155)

Parameters	n(%)
Age(Mean±SD)	**33.80±9.26 years**
Gender	
Male	75(48.39)
Female	80(51.61)
Marital Status	
Married	99(63.87)
Unmarried	56(36.13)
Education	
Matric or more	123(79.35)
Below matric	32(20.62)
HAM-D Score	
Mild to Moderate Depression	97(62.58)
Severe Depression	58(37.42)
Range	14.00
Minimum	8.00
Maximum	22.0
Serum Folate Levels	
Normal	57(36.77)
Borderline	45(29.03)
Deficiency	53(34.19)
Mean±SD	3.10±1.4 ng/ml

Table-II: Comparison of Folate Deficiency and HAM-D Scores (n=155)

	Serum Folate Levels	HAM-D score		*p*-value
		Mild-Moderate Depression n(%)	Severe Depression n(%)	
Serum Folate Levels	Normal	57(58.8)	0(0)	<0.001
	Borderline	12(12.4)	33(56.9)	
	Deficiency	28(28.9)	25(43.1)	

Among 97 cases had mild–moderate depression (58.8% cases had normal, 12.4% cases had borderline, and 28.9% cases had folate deficiency), while 58 patients had severe depression (56.9% cases had borderline folate levels and 43.1% cases had folate deficiency), the frequency of borderline–folate deficiency was

statistically higher in patients with severe depression) *p*-value<0.001 (Table-II). When data were categorised for age, gender, marital status and education level, a significant difference was found in serum folate in patients with mild to moderate and severe depression *p*-value<0.05 (Table-III).

Table-III Comparison of Folate Deficiency in HAM-D Score with Demographic Variables (n=155)

Parameters	Categories	Serum Folate Levels	HAM-D Score		*p*-value
			Mild to Moderate Depression n(%)	Severe Depression n(%)	
Age (years)	18-35	Normal	35(57.9)	0(0)	<0.001
		Borderline	8(14)	18(60)	
		Deficiency	16(28.1)	12(40)	
	36-50	Normal	24(60)	0(0)	<0.001
		Borderline	4(10)	15(53.6)	
		Deficiency	12(30)	13(46.4)	
Gender	Male	Normal	28(59.6)	0(0)	<0.001
		Borderline	4(8.5)	20(71.4)	
		Deficiency	15(31.9)	8(28.6)	
	Female	Normal	29(58)	0(0)	<0.001
		Borderline	8(16)	13(43.3)	
		Deficiency	13(26)	17(56.7)	
Marital Status	Married	Normal	43(62.3)	0(0)	<0.001
		Borderline	6(8.7)	18(60)	
		Deficiency	20(29)	12(40)	
	Unmarried	Normal	14(50)	0(0)	<0.001
		Borderline	6(21.4)	15(53.6)	
		Deficiency	8(28.6)	13(46.4)	
Education	Below Matric	Normal	11(68.8)	0(0)	<0.001
		Borderline	1(6.2)	6(37.5)	
		Deficiency	4(25)	10(62.5)	
	Matric/Above	Normal	46(56.8)	0(0)	<0.001
		Borderline	11(13.6)	27(64.3)	
		Deficiency	24(29.6)	15(35.7)	

DISCUSSION

In the current study, mean age of patients was 33.80±9.26, with minimum and maximum ages being 18 and 50 years. There were 75(48.4%) males and 80 (51.6%) females, with a slightly higher female-to-male ratio. Jeon et al. showed that 36.1% of men and 36.4% of women experienced symptoms of depression.[16] Symptoms of depression were found to be less when serum folate levels were high in men.[17] Hence, it supports the observation that Low serum folate is related to an increased prevalence of depression in men, as is evident in the result of our study.

In a study conducted by Zheng *et al*. Depression was assessed by using Patient Health Questionnaire (PHQ), while the presence of depressive symptoms was defined as PHQ total score ≥10. The main findings revealed that women showed higher overall mean PHQ scores than men. It was interesting to note that these higher PHQ scores in women were inversely associated with folate levels.[18]

The results of this study correlate with the findings of a population-based survey by Markkula *et al*. to find out the associations of folate with depression. In this study total of 278 persons with depressive symptoms were assessed for Folate blood levels. After adjusting for age, gender, cardiovascular disease, and functional disability, it was observed that low folate levels were evident in persons exhibiting depressive symptoms.[19]

Observational studies conducted on adults have also highlighted that the risk of developing depression or higher levels of depressive symptoms increases with low serum folate levels in the body. Another study on 96 adult Chinese also observed low folate levels associated with depression. However, it is also important to highlight that some studies have shown an association between low folate levels and depressive symptoms but with inconsistent findings.[20]

This cross-sectional study indicated that lower folate is a significant risk factor in the development of depression. Therefore, mental health professionals must understand the interactive effects of nutritional

elements, especially folate, as it can prove a protective step against potential brain neurotoxicity that can lead to depressive symptoms. Furthermore, specific reports suggest that adding folate supplements along with anti-depressants can increase the therapeutic effects of the prescribed regimens.

CONCLUSION

Results of this study highlight that the frequency of borderline-folate deficiency was statistically higher in cases with severe depression.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AAB: & SA: Conception, study design, drafting the manuscript, approval of the final version to be published.

SAK: & HR: Data acquisition, data analysis, data inter-pretation, critical review, approval of the final version to be published.

FH: & TBN: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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