ORIGINAL ARTICLE

Homocysteine and Vitamin D Levels: An Association with Depression and its Severity

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ABSTRACT

Objective: To determine the association of serum Homocysteine and serum vitamin D levels with depression and its severity.

Study Design: Cross-sectional study.

Place and Duration of Study: The study was conducted at the Department of Psychiatry, Armed Forces Institute of Mental Health (AFIMH), Rawalpindi, Pakistan, from December 2021 to May 2022.

Methods: We recorded demographic data, including age, gender, and socioeconomic status of consecutively sampled 155 subjects. Depression and its severity was assessed by applying the Urdu version of the Hamilton Depression Rating Scale (HAM-D U). Blood samples were collected to assess serum homocysteine and serum vitamin D before commencing any treatment for depression; these samples were assessed at the Armed Forces Institute of Pathology (AFIP Rawalpindi).

Results: The mean Hamilton Depression Rating Scale (HAM-D U) score was 17.14 ± 4.29 with minimum and maximum scores as 8 and 22. There were 97 (62.6%) cases that had mild to moderate depression, and 58 (37.4%) patients had severe depression. The frequencies of intermediate to severe Homocysteine levels were statistically higher in individuals with severe depression ($p < 0.001$), while vitamin D deficiency was also statistically higher in individuals experiencing severe depression ($p < 0.001$).

Conclusion: Raised serum homocysteine levels and deficiency of serum vitamin D is associated with the severity of depression.

Keywords: *Depression, Homocysteine, HAM-D, Vitamin D.*

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Introduction

Considering global burden of disease and disability depression is the second most important factor for the increase in disability due to deterioration in social and occupational functioning.[1] Frequency of depression ranges between 4.2 and 17% in Pakistan as reflected in a systematic review that anxiety and depression to be as high as 34% in the Pakistani population.[2] Depression increases the risk of negative cognitions, life experiences, problems in physical health, deterioration in professional activities, defective social interactions, drug dependence, problems with law, and suicide.[3] It has been observed that diet and dietary nutrients play important role in maintaining our mood and there deficiency can lead to development of depression.[4] In this context, nutrients like selenium, zinc, omega-3 polyunsaturated fatty acids, magnesium, vitamins B, homocysteine, and vitamin D are important.[5] Research suggests that processed meal/food, intake

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of refined grains, and meals high in sugar and fat content is closely associated with the development of depression.[6] Homocysteine is a sulphurated amino acid that is derived from methionine found in poultry, eggs, meat, fish, and cheeses. Research indicates that men and women with elevated homocysteine are associated with depression. Still, other studies suggest otherwise and find no association of depression with the serum homocysteine levels.[7] These contradicting results can be because, at different ages there are different types of depression, in addition to genetic predisposition, brain disease, and random technique for sample selection leading to a heterogeneous sample for the study.[8] Vitamin D, or calciferol, is a fat-soluble steroid hormone helps in the absorption of calcium from the gut into the bloodstream. Vitamin D is of two main forms: Vitamin D2 (ergocalciferol), which is synthetic and added to different foods, and vitamin D3 (cholecalciferol), which is synthesized naturally in the skin of humans from 7-dehydroxycholesterol.[9] Serum levels of vitamin D have shown to be associated with metabolic diseases including diabetes mellitus, obesity, and hypertension in addition to neuropsychiatric ailments such as cognitive impairment, Alzheimer's disease, Parkinson's disease, schizophrenia, and depression.[9] Although not conclusive but it seems that vitamin D deficiency leads to imbalance in the calcium homeostasis of intracellular and extracellular compartments leading to disequilibrium between glutamate and GABA pathways, consequently paving the way for the development of depression. Researchers have highlighted that vitamin D levels are low in individuals exhibiting depression compared to normal individuals, suggesting a greater risk of developing depression with low vitamin D levels.[10] Furthermore, different studies have also found that serum levels of vitamin D and depression are inversely proportional.[8]

The aforementioned results are a depiction of the western population that cannot be translated conclusively on to our local population. Unfortunately, there is scarcity of local literature on the subject therefore, we aim to establish relationship between serum homocysteine and vitamin D with depression in a local Pakistani sample, so as to ascertain true picture regarding management planning.

Methods

This cross-sectional study was conducted at the Department of Psychiatry, Armed Forces Institute of Mental Health (AFIMH), Rawalpindi, Pakistan from December 2021 to May 2022 after approval of ethical review committee held on November 06, 2021 vide Serial No. 00/11/21. A total sample size of 155 was obtained using the WHO sample size calculator based on the results of the study conducted by Esnafoglu and Ozturan where the anticipated population proportion was 11.3.[11] We consecutively sampled 155 subjects using a convenience non-probability sampling technique. All newly reporting patients of both genders aged 18-50 years having clinical depression were diagnosed using ICD-10 criteria included, and severity was assessed using the HAM-D scale.[12-13] Patients taking any vitamin D or homocysteine supplements in the last three months, Patients with medical conditions that are associated with vitamin D deficiency (including megaloblastic anemia; hyperparathyroidism and Crohn's disease; celiac disease) Patients with medical conditions that are associated with raised serum homocysteine levels and Patients on medications that interfere with vitamin D metabolism were excluded.

Hamilton Depression Rating Scale – Urdu version (HAM-D U) was used to ascertain severity of depression from a total score of 50.[13-14] This depression scale has 21 items but Scoring is done on the first 17 items. On average, it usually takes 15-20 minutes to complete the questionnaire and score the results. Nine items are scored from 0-2. Eight items are scored on a 5-point scale (0-4), 9 items are scored as: 0 – absent, 1 – doubtful or trivial; 2 – present, 8 items are scored as: 0 – absent; 1 – mild; 2 – moderate; 3 – severe; 4 – incapacitating. To obtain a Depression Severity, scoring is done from a total of 50. Scores are reflected as follows: 8-13 mild; 14-18 moderate; 19-22 severe; equal to or greater than 23 very severe. Mild to moderate depression (score 0 – 18) was designated as Group A, while Group B included depression (score > 18).

Blood samples were collected for homocysteine and

vitamin D levels and sent to the Armed Forces Institute of Pathology (AFIP) for assessment. Based on the American Heart Association, serum homocysteine levels were considered normal (5 – 15 mol/l), moderate (16 – 30 mol/l); intermediate (31-100 mol/l), and severe (> 100 mol/l). Individuals with serum vitamin D less than 25 nmol/l were considered to have vitamin D deficiency and were categorized as having normal or deficient vitamin D levels accordingly.

Software SPSS 23 was used for analysis. The severity of depression, along with the level of homocysteine and vitamin D deficiency, gender, educational level, and marital status, were depicted as frequencies and percentages. Any difference in the frequency distribution of Vitamin D and homocysteine was compared between the depression groups by applying the chi-squared test. Mean and standard deviation of homocysteine, vitamin D and HAM-D scores of all participants were described. Stratification was used to control confounding variables like age, gender, severity of depression, marital status, and educational status, while Chi-squared test was used for the statistical significance level which was taken as 5% ($p \leq 0.05$).

Results

Participants' mean age in this study was 33.80 ± 9.26 with a range of 18 to 50 years, out of which 87(56.1%) were 18 to 35 years of age while 68(43.9%) were between 36 to 50 years of age, male participants were 75(48.4%) and 80(51.6%) were females and out of total 155 participants 99 (63.9%) were married and 56(36.1%) were un-married while 32(20.6%) had education below matric and 123 (79.4%) were matriculate or above. Participants' mean score on HAM-D for depression was 17.14 ± 4.29 that, ranged between 8 and 22. 97(62.6%) participants scored mild to moderate levels of depression and 58(37.4%) exhibited severe depression. Mean serum homocysteine levels were 59.33 ± 31.81 µmol/L, with a minimum and maximum value of 5.68 and 109.27µmol/L respectively. 20 (12.90%) participants had normal serum homocysteine levels, 17 (10.97%) had moderate serum levels, 107 (69.03%) had intermediate serum levels and 11 (7.10%) participants had severe levels of serum homocysteine. Mean serum vitamin D levels among participants was 41.82 ± 23.69 nmol/L, ranging between 18.12 and 92.55 nmol/L. 66 (42.58%) participants had deficient vitamin D serum levels, 66 (42.58%) had insufficient vitamin D in their serum and 23 (14.84%) had sufficient serum levels of vitamin D (Table 1).

Table 1: Severity of depression with serum Homocysteine and serum vitamin D levels

S.no	Category	n (%)
1	**HAM-D Score**	
	Mild to Moderate Depression	97 (62.58)
	Severe Depression	58 (37.42)
	Range	14.00
	Minimum	8.00
	Maximum	22.0
2	**Serum Homocysteine Levels**	
	Normal	20 (12.90)
	Moderate	17 (10.97)
	Intermediate	107 (69.03)
	Severe	11 (7.10)
	Mean ± SD	59.33 ± 31.81µmol/L
3	**Serum Vitamin D levels**	
	Deficient	66 (42.58)
	Insufficient	66 (42.58)
	Sufficient	23 (14.84)
	Mean ± SD	41.82 ± 23.69 nmol/L

Participants who had mild to moderate depression when compared with serum homocysteine levels it was observed that 20 (20.6%) had normal levels, 17 (17.5%) had moderate, 60 (61.9%) intermediate and none had severely increased serum homocysteine

levels, on the other hand, those participants who exhibited severe depression 47 (81%) had intermediate serum homocysteine levels, 11 (19%) had raised serum homocysteine levels. In contrast, none of the participants exhibiting severe depression had normal or moderate serum homocysteine levels (p<0.001). when serum vitamin D levels were compared with mild to moderate depression among participants it was observed that 44 (45.4%) had deficiency, 30 (30.9%) had insufficient serum vitamin D while 23 (23.7%) had sufficient serum vitamin D levels on the other hand among participants with severe depression 22 (37.9%) had deficient serum vitamin D, 36 (62.1%) had insufficient serum vitamin D while none had sufficient serum levels of vitamin D (p<0.001) as shown in Table 2.

Table 2: Comparison of serum Homocysteine and Vitamin D levels with HAM-D scores

Category	Serum Levels	HAM-D score		*P* value
		Mild-Moderate Depression n (%)	Severe Depression n (%)	
Homocysteine	Normal	20 (20.6)	0 (0)	<0.001
	Moderate	17 (17.5)	0 (0)	
	Intermediate	60 (61.9)	47 (81)	
	Severe	0 (0)	11 (19)	
Vitamin D	Deficient	44 (45.4)	22 (37.9)	<0.001
	Insufficient	30 (30.9)	36 (62.1)	
	Sufficient	23 (23.7)	0 (0)	

For analysis among participants with mild to moderate and severe depression, when data were stratified for age and gender, significant difference was found in serum homocysteine and vitamin D levels ($p < 0.05$). The mean homocysteine level was statistically higher in patients with severe depression as compared to mild to moderate levels of depression ($p < 0.05$) Table 3.

Table 3: Association of HAM-D score and serum Homocysteine levels with Age and Gender

S. No	Variables	Category	Homocysteine levels	HAM-D Score		*P* value
				Mild to Moderate Depression n (%)	Severe Depression n (%)	
1	**Age (years)**	18-35	Normal levels	11 (19.3)	0(0)	<0.001
			Moderate	7 (12.3)	0 (0)	
			Intermediate	39 (68.4)	26 (86.7)	
			Severe	0 (0)	4 (13.3)	
		36-50	Normal	9 (22.5)	0 (0)	<0.001
			Moderate	10 (25)	0 (0)	
			Intermediate	21 (52)	21 (75)	
			Severe	0 (0)	7 (25)	
2	**Gender**	Male	Normal	13 (27.7)	0 (0)	0.001
			Moderate	10 (21.3)	0 (0)	
			Intermediate	24 (51.1)	25 (89.3)	
			Severe	0 (0)	3 (12.2)	
		Female	Normal	7(14)	0 (0)	<0.001
			Moderate	7 (14)	0 (0)	
			Intermediate	36 (72)	22 (73.3)	
			Severe	0 (0)	8 (26.7)	

While mean vitamin D level was statistically lower in patients with severe depression as compared to mild-moderate depression ($p < 0.05$) as shown in Table 4.

Table 4: Correlation of HAM-D score and serum vitamin D levels with Age and Gender

S.no	Variables	Category	Vitamin D levels	HAM-D Scores		*P* value
				Mild to moderate depression n (%)	Severe depression n (%)	
1	**Age (years)**	18-35	Deficient	25 (43.9)	11 (36.7)	0.002
			Insufficient	18 (31.6)	19 (63.3)	
			Sufficient	14 (24.6)	0 (0)	
		36-50	Deficient	19 (47.5)	11 939.30	0.006
			Insufficient	12 (30)	17 (60.7)	
			Sufficient	9 (22.5)	0 (0)	
2	**Gender**	Male	Deficient	23 (48.9)	12 (42.9)	0.002
			Insufficient	12 (25.5)	16 (57.1)	
			Sufficient	12 (25.5)	0 (0)	
		Female	Deficient	21 (42)	10 (33.3)	0.005
			Insufficient	18 (36)	20 (66.7)	
			Sufficient	11 (22)	0 (0)	

Discussion

Data of the current study show that out of total sample, the majority of participants were married and were females. The mean age of participants was thirty-three years plus minus nine years, and the majority of individuals had educational qualification of matric or above. Hoepner CT et al. in his study and Moradi F in his systematic review noted that in a total sample of one hundred and fifty-five more than sixty percent of the participants experienced mild to moderate level of depression and only thirty-seven percent of individuals experienced depression of severe level. While seventy percent of individuals had intermediate level of serum homocysteine, seven percent had severely raised homocysteine levels and in twenty percent serum homocysteine level ranged from normal to moderate.[15,16] similarly Menon V observes that about eighty-five percent of individuals had insufficient to deficient serum vitamin D levels.[17] Furthermore Menon V and Moradi F noted that those individuals in whom serum homocysteine levels were normal or moderately raised none of them had severe symptoms of depression instead they experienced mild to moderate level of depression. On the other hand individuals with intermediate to severely raised serum homocysteine levels experienced severe level of depressive symptoms indicating that homocysteine levels are strongly associated with depression.[16,17]

Bigman G in his study noted that Vitamin D and its metabolites (D3 and D2) deficiency is associated with depression symptoms among adults.[18] Similarly, our analysis also highlights that individuals exhibiting depressive symptoms had insufficient or deficient serum vitamin D levels, on the other hand individuals with sufficient serum vitamin D levels did not exhibit severe level of depression. Further studies are needed as to determine why depression occurs in Vit D deficiency and if it is directly co related with etiology of depression as well.

Serum homocysteine levels, serum vitamin D levels and severity level of depression were compared with different demographic variables for further analysis. This comparison is in conformity with the study results of Paduchová Z et al. it is noted that raised serum levels of homocysteine and depression had significant correlation with male gender and those individuals who had educational qualification below secondary level, while this correlation was highly significant in relation to age, female gender, married individuals and individuals with educational qualification of matric or above.[19] Interestingly, no significant correlation was found with individuals

who were unmarried. As for the vitamin D levels study by Esnafoglu E and the data of this study indicate that reduced serum vitamin D levels were significantly correlated with depression among married individuals and those who had an educational level of matric or more while age, gender, being unmarried and individuals having educational level below matric showed no significant correlation with depression in presence of low serum vitamin D levels.[11]

Conclusion

Based on the results of this study it can be concluded that intermediate to severely raised serum Homocysteine levels are highly correlated with severity of depression. Similarly, deficiency or insufficiency in the serum vitamin D levels is strongly associated with severity of depression.

Limitation of Study

Authors acknowledge that inferences cannot be done alone on descriptive study and need application of analytical and deductive reasoning to draw a meaningful reasoning from the provided data. It cannot be conclusively commented upon whether serum vitamin D levels lead to development of depression or is it depression itself that leads to raised serum homocysteine and reduction in serum vitamin D levels.

Authors Contribution

AAB: Idea conception, study designing, data collection, manuscript writing and proof reading

SK: Study designing, data analysis, results or interpretation, manuscript writing and proof reading

HR: Idea conception, data collection, data analysis, results and interpretation

TBN: Study designing, data analysis, results or interpretation, manuscript writing and proof reading

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