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Original Article

Serum Vitamin-D Levels and Severity of Clinical Depression in Patients of a Psychiatric Clinic in Pakistan

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ABSTRACT

Vitamin D deficiency is often correlated with nervous system disorders like major depression, Parkinson's disease and dementia. While much of the clinical literature suggests its association with clinical depression, very few studies have looked into the relationship between vitamin D levels and clinical depression severity. **Objectives:** To find out the association between vitamin D levels in patients suffering from different severities of clinical depression with the confounding socio-cultural factors of a third-world country i.e., Pakistan. **Methods**: The cross-sectional study was conducted in Lady Reading Hospital, Peshawar for five months with convenience sampling. **Results:** Overall, the study had 132 (36.57%) males and 229 (63.43%) females, and 236 diagnosed cases of Clinical Depression. In terms of Vitamin D levels, 242 (67.04%) had deficient, while 77 (21.33%) and 42 (11.63%) had insufficient and normal vitamin D levels, respectively. There was a statistically significant difference in the serum Vitamin D levels between at least two groups ($F(3,232)=[38.64]$, $p<0.05$). **Conclusions:** Vitamin D levels showed a dose-dependent, inverse relation with the severity of clinical depression in the Pakistani population.

INTRODUCTION

In recent years, Vitamin D has gained much attention among the public at large and most medical specialties in specific. This is because it is involved in many physiologic functions, some of which are yet to be discovered [1]. It has mainly two forms, i.e., D2, gained from plants, and D3, from fish and eggs. While the dietary sources are important, 80-90% of its supply comes from the UV light from the sun, in a process that converts 7-dehydrocholesterol to Vitamin D. At present, we have an epidemic of Vitamin D deficiency in the world, which is unrelated to the gender, age or racial factors. In Europe alone, 40% of its people have vitamin D deficiency, which is thought to increase with time [2]. Furthermore, 13% have severe Vitamin D deficiency, which prompts supplementation. Even the U.S shows a similar statistic of 41.6%, furthering its argument [3]. In third-world countries, women of child-bearing age have multiple nutritional deficiencies, and vitamin D is no exception [4]. Furthermore, the statistics in these countries are far more alarming than the developed nations as this links directly to infant mortality and severe disease. The incidence of vitamin D deficiency is usually associated with an inadequate intake of Vitamin-D-containing foods, low sunlight exposure, and obesity, leading to adipose tissue sequestration [5, 6]. Although inadequate intake would make an excellent causal argument in the case of third-world countries, decreased sunlight exposure and obesity

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do not [7]. This is because people living in these countries usually have higher exposure and lower prevalence of obesity than in the U.S. and Europe, which makes the population set unique. This population has wide physiological and psycho-social variation versus the usually taken U.S. or European-based populations, which is well established in the literature. Hence, one can assume that the disease manifestations of Vitamin D deficiency might also be different. These can include respiratory, dermatological, gastrointestinal, and neuropsychiatric issues, in addition to the traditionally highlighted, musculoskeletal ones [1, 8, 9]. Vitamin D is essential for the good health of the nervous system and is often inversely correlated with nervous system disorders like Major Depression, Parkinson's disease and Dementia, etc [10, 11]. Among these diseases, we aimed to investigate Clinical Depression and its relation to Vitamin D deficiency. This is because, in addition to being a debilitating disease, it can cause psychosomatic symptoms like chronic fatigue syndrome, hyperventilation, irritable bowel syndrome, unexplained abdominal pain, tension headache, chronic pelvic pain, and atypical facial and chest pain [12, 13]. Hence, somatization can lead to a diagnostic paradox for clinicians that can overlap with many systemic symptoms, especially Vitamin D deficiency symptoms. The problem is magnified when different severities of Clinical Depression are taken into account, as mild Depression is more likely to be masked by psychosomatic symptoms imitating Vitamin D deficiency. Therefore, the line between clinical Depression in the Pakistani population caused by psycho-social factors versus biological factors, specifically, a vitamin D deficiency, is blurred. While most of the epidemiological literature hypothesizes that vitamin D deficiency might be related to clinical depression, very few studies have looked into the relationship between vitamin D levels and clinical depression severity. To the best of our knowledge, no study has been reported on the association between vitamin D levels in patients suffering from different severities of Clinical Depression with the confounding socio-cultural factors of a third-world country i.e., Pakistan.

METHODS

After approval from the IRB, ethical board, a prospective, cross-sectional study was conducted in the Department of Neurology and Psychiatry in Lady Reading Hospital, Peshawar, for five months. Based on significance level of 0.05 and power of 80%, the sample size was calculated using OpenEpi software, applying the formula: Sample size $n = [DEFF*Np(1-p)]/ [(d2/Z21-\alpha/2*(N-1)+p*(1-p)]$. The sample size came out to be 384. We selected the patients based on specific diagnostic and ethical criteria: 1. Adult patients (18 and higher age), 2. Suffering from Unipolar Clinical Depression, as per PHQ-9, 3. Willing to participate in the study, 4. Pregnant patients were excluded; 5. Patients with co-morbid diagnosed psychiatric conditions were also excluded. The diagnosis of clinical Depression is made based on the DSM-V criteria and employs ab already validated questionnaire called the PHQ-9. The PHQ-9 is a self-rating tool widely used in clinical research to diagnose and monitor clinical Depression. The tool was formed in 1999 by Spitzer et al., and it monitors the presence and severity of Depression based on the DSM criteria. We used a modified version of the PHQ-9, which was first translated to the national language, i.e., Urdu, and double-checked for cultural fitness with the help of a Pakistani Expert. The meaning and layout were maintained to the original version, and the subject matter was kept in line with cultural astuteness, based on Research and Development Health Corporation (RAND). The internal reliability of the modified questionnaire was tested using a pilot study of 31 patients, and the Cronbach's alpha value was >0.92; hence we proceeded to carry out the investigation further. Depression Severity was established as: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe. Patients who presented in the outpatient clinic of Lady Reading Hospital were included. Complete physical examination was done for all the patients to rule out organic causes of the diseases, and a certified psychiatrist undertook the psychiatric interviews to assess their mental state. The affective symptoms were evaluated, and the diagnosis of clinical Depression was made based on the DSM-V criteria. Afterward, the patients were invited to be checked for serum 25-Hydroxy Vitamin D concentrations under a fasting state using the Electrochemiluminescence method. Reference ranges included: equal to, or more than 30 ng/ml as normal, less than 20 ng/ml as deficient, and between 21-29, ng/ml was defined as insufficient. Terms of non-disclosure were ensured and mentioned to all the participants. Out of the 384 patients approached, 361 patients fulfilled the inclusion criteria, but 24 were lost on follow-up; hence, 337 patients participated in the study. Among that number, 101 patients were later diagnosed with co-morbid psychiatric illnesses that did not fulfill the inclusion criteria; hence a total of 236 patients were finally selected. SPSS version 26.0 was used for the data analysis, and the results were reported. Descriptive variables were reported as frequencies and percentages, while continuous variables were reported as means with standard deviation (S.D.). Normality for all the continuous variables was also checked, by using the skewness and kurtosis method and confirmed it by checking the presentation with a histogram. Statistical tests including the Chi-square test, independent student t-test, and

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logistic regression were performed as per data needs. A p-value of <0.05 was taken as significant.

RESULTS

Overall, our study had 132 (36.57%) males and 229 (63.43%) females, and 236 diagnosed cases of clinical depression. In terms of Vitamin D levels, 242 (67.04%) had deficient, while 77 (21.33%) and 42 (11.63%) had insufficient and normal vitamin D levels, respectively. A total of 162 (44.88%) patients had normal BMI, while 85 (23.55%) were underweight and 114 (31.58%) were either overweight or obese (Table 1).

Variables	Number (%)
Gender	
Male	132 (36.57%)
Female	229 (63.43%)
Diagnosis	
Clinical Depression	236 (65.37%)
Other	125 (34.63%)
Vitamin D levels	
Deficient	242 (67.04%)
Insufficient	77 (21.33%)
Normal	42 (11.63%)
BMI	
Normal	162 (44.88%)
Overweight	114 (31.58%)
Underweight	85 (23.55%)

Table 1: Demographics and General Characteristics

Mild depression was the most common severity observed with a total of 143 (39.61%) patients, while moderate depression affected 46 (12.74%), moderately severe 31 (8.59%) and a total of 16 (4.43%) patients suffered from severe depression (Table 2).

Severity of Clinical Depression	Number (%)
Mild	39.61 (143%)
Moderate	12.74 (46%)
Moderately severe	8.59 (31%)
Severe	4.43 (16%)

Table 2: Frequency of different severities of clinical depression

We found no statistically significant difference between gender, presence or absence of clinical depression, and BMI with the status of vitamin D deficiency via the Chi-Square Test (p>0.05). However, the serum Vitamin D values for mild depression were 20.26 ± 14.42, while for moderate depression, it was 13.87 ± 9.21, moderately severe depression showed 10.63 ± 6.40, and severe depression showed a 2.73 ± 2.06 level. A one-way ANOVA was performed to compare vitamin D levels (independent variable) with the severity of clinical depression (dependent variable). It revealed that there was a statistically significant difference in the serum Vitamin D levels between at least two groups ($F(3,232) = [38.64]$, $p < 0.05$). Levene's test showed that the variances among the different Vitamin D levels were not equal. Therefore, Welch and Games-Howell tests were applied for posthoc analysis instead of Tukey HSD tests, which showed that the mean value of serum Vitamin D was significantly different between mild and moderate, moderately severe, and severe groups. (p=0.003, 95% C.I. = [1.65, 11.12]). A similar trend was observed between moderate and severe (p=0.00, 95% C.I. = [7.26, 15.00]) and moderate-severe to severe groups (p=0.00, 95% C.I. = [4.52, 11.29]). There was no statistically significant difference in Vitamin D levels between moderate and moderately severe (p=0.27) depression (Table 3, 4).

Variable		Vitamin D Deficiency	Vitamin D Insufficiency	Sufficient	Total	p-value
Gender	Male	83	34	16	133	0.125
	Female	170	33	25	228	
Diagnosis	Clinical Depression	158	37	39	234	0.08
	Other	94	29	4	127	
BMI	Normal Range	52	21	11	84	0.28
	Overweight	17	39	21	236	
	Underweight	623	8	10	41	

Table 3: Chi-square Test – Vitamin D status with gender, diagnosis and BMI

Mild	Moderate	Moderately Severe	Severe
Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
20.26 ±14.42	13.87 ± 9.21	10.63 ± 6.40	2.73 ± 2.06

Table 4: Vitamin D Levels and Severity of Clinical Depression

DISCUSSION

Our study intended to find the association between vitamin D levels and the severity of clinical depression, in a Pakistani population. This is different from much of the published literature in the aforementioned population that mainly shows the mere presence or absence of the illness. Our study also looked into the relationship between vitamin D deficiency and obesity, as it has been suggested to be an important covariate [14, 15]. The ANOVA findings demonstrate a dose-response gradient of vitamin D deficiency and depression, where the severity of clinical depression is inversely related to the levels of serum vitamin D. These findings echo the published studies by Esnafoglu et al., and Di et al., in which the tested population was predominantly ethnic white [16, 17]. The similar result indicates that even though, depression has multivariate causality, the vitamin D deficiency is inversely related to the severity of clinical depression, irrespective of the patient ethnicity and economic status in the country [17, 18]. Hence, this trend seen in first world countries is also the same in third world countries. As far as obesity and vitamin D is concerned, our study did not show any significant relationship between the two. This contrasts with many other studies in which obesity was significantly

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associated with vitamin D deficiency [14, 19]. As mentioned in the work done by Vranić et al., obese populations have a high tendency to have vitamin D deficiency. This is most often attributed to the volumetric dilution into the body tissues, including fat and muscle [20]. While it is difficult to presume the exact reason for which obesity did not have a significant relation to vitamin D levels in our target population, there are likely some important physiological processes behind it, that require further exploration. Even though there seems to be a uniform relation between vitamin D levels and the severity of clinical depression, epidemiological evidence is disputed for the use of vitamin D for treating it. There are some studies, including a clinical trial that support the use of Vitamin D supplementation for the reduction of symptoms of clinical depression [21, 22]. However, other studies revealed the opposite results, showing that vitamin D supplementation does not contribute to the prevention or treatment of clinical depression [23-25]. Therefore, even though, serum vitamin D levels have an inverse correlation with clinical depression, the evidence in support of universal supplementation in it is not strong. This is a possible area of further research that needs to be explored so that subgroups, who are likely to benefit from supplementation in treatment can be identified so that patients may maximally benefit from this approach [26].

CONCLUSIONS

Vitamin D levels showed a dose-dependent, inverse relation with the severity of clinical depression in the Pakistani population. Furthermore, Vitamin D levels did not have any significant association with obesity in the population. In the long run, clinical trials with different patient ethnicities can open doors for identification and possible addon supplementation treatments for clinical depression.

Conflicts of Interest

The authors declare no conflict of interest.

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