

## Assessment of Vitamin D Role in Depression

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### Abstract

**Background:** Depression is a devastating disease that adversely affects all aspects of one's existence. There is some evidence that low circulating concentration of serum 25-hydroxyvitamin D [25(OH)D], the marker for Vitamin D status, is associated with mood disorders, including major depressive disorder.

**Aim of Study:** The aim of this work is to investigate the association between serum Vitamin D concentrations and depression and to evaluate the correlation between the concentrations of Vitamin D and severity of depression.

**Subjects and Methods:** This study was conducted on 66 patients suffering from depression, and 22 apparently healthy individuals as controls. Complete psychiatric interview; with application of Beck Depression Inventory II (BDI-II) Scale for diagnosis and assessment of the severity of depression was done. Laboratory investigations including kidney function tests, liver function tests, serum total calcium, phosphorus and serum Vitamin D (25-OH Vitamin D3/D2) was done for all subjects.

**Results:** 21, 23 and 22 patients had mild, moderate and severe depression respectively. There was statistically very high significant decrease in Vitamin D level in patients group compared to control group. In patients group, 40.9% of patients had Vitamin D deficiency (serum 25(OH)D <12ng/mL), 33.3% had Vitamin D insufficiency (serum 25(OH)D ranged from 12 to 20ng/mL), and 25.8% had sufficient level of Vitamin D (serum 25(OH)D >20ng/mL). There was statistically significant decrease of Vitamin D levels in female patients group compared to male patients group. There was statistically significant negative correlation between BDI-II score and Vitamin D level in patients group.

**Conclusion:** The finding of this study revealed evidence of an association between low 25(OH)D, a marker of Vitamin D status, and depression, suggesting a direct effect of Vitamin D on development of depression. There was an association between low Vitamin D status and the severity of depression. Vitamin D deficiency was more pronounced in female patients than male patients.

**Key Words:** Depression – Vitamin D – Depression severity – Beck depression inventory scale.

### Introduction

**DEPRESSION** is a common illness worldwide and it results from a complex interaction between social, psychological, and biological factors [1]. It is an etiologically heterogeneous group of brain disorders characterized by a wide range of symptoms that reflect alteration in cognitive, psychomotor and emotional process [2]. Depression is a common mental disorder that affects both males and females in every age group and is found across cultures. An investigation into the global burden of disease found depressive disorders to be the second leading cause of disability worldwide [3]. Vitamin D (D represents D2, D3, or both), known as the “sunshine vitamin,” and is a secosteroid produced endogenously in the skin from sun exposure or obtained from foods [4]. It is necessary for essential biological functions such as bone and mineral metabolism, muscle function, psychological function and immunity [5]. There is accumulating evidence of the association of serum (25(OH)D) levels with a wide range of physiological outcomes such as bone health, cardiovascular diseases, diabetes, hypertension, metabolic syndrome, and cancer [6]. Vitamin D receptors are present in many different types of cells, including neurons and glial cells. Most importantly, Vitamin D is accepted for its neurosteroid activity and impact on brain serotonin (a neurotransmitter critical to emotional health), suggesting a possible role in mood regulation [7]. Vitamin D is also involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development making it biologically plausible that Vitamin D might be associated with depression [8].

### Material and Methods

**Study design:** This is a hospital based prospective study.

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**Study area:** The study was conducted at Psychiatry Department, Assiut University. The study was done in the Clinical Pathology Department of Assiut University Hospital in the years from 2015 to 2016.

**Study populations:** There were two groups of participants in this study. Group 1 (case group): Comprised 66 patients suffering from depression recruited from Psychiatry Department, Assiut University. Group 2 (control group): 22 normal subjects. These were age and sex matched with the test group.

**Sample size:** A total of 88 subjects were studied. These included 66 patients suffering from depression (case group) and 22, age and sex matched normal subjects (control group).

**Ethical approval:** All subjects were informed about the aim of the study and gave their consent.

**All patients were subjected to personal and psychiatric history and complete medical examination:**

To assess the severity of depression, the 21-Beck Depression Inventory Scale for Depression-II (BDI-II) was used [9]. The severity of depression was categorized to mild, moderate and severe according to age and gender.

Group	Age	No or minimal depression	Mild depression	Moderate depression	Severe depression
Female (18-21) yrs		0-20	21-29	30-37	38-63
Male (18-21) yrs		0-19	20-27	28-34	35-63
Female (22-60) yrs		0-20	21-31	32-41	42-63
Male (22-60) yrs		0-15	16-24	25-33	34-63

**Mild depression:** Twenty one (21) patients, ten were females and eleven were males.

**Moderate depression:** Twenty three (23) patients, seventeen were females and six were males.

**Severe depression:** Twenty two (22) patients, ten were females and twelve were males.

#### Exclusion criteria:

Patients with (liver, kidney diseases, GIT problems as Crohn's disease and malabsorption, patients on anticonvulsant drugs, pregnant and lactating females, psychiatric disorders other than depression or those with comorbid diagnosis).

#### Procedure:

**Sample collection and storage:** Five ml were collected into plain tube. Blood was allowed to clot for 15 minutes at 37 °C and sera were separated

by centrifugation at 3000rpm for 10 minutes. The separated sera were inspected to ensure that they were clear and non-hemolyzed or lipaemic. Serum was divided into two aliquots, one aliquot was used for determination of the routine laboratory investigations and the other aliquot was stored at -20°C till time of assay. Liver function tests, kidney function tests, total calcium, phosphorus and serum Vitamin D level was done.

#### Laboratory assays:

**1- Routine investigations:** Serum Liver function tests, kidney function tests, total calcium and phosphorus (for patients and controls): They were performed on auto analyzer Modular (Roche) USA.

**2- Specific tests:** Vitamin D level (for patients and controls): Was done on Alegria® (ORGENTEC Diagnostic GmbH-Germany), using 25-OH Vitamin D3/D2-ORG 270Orgentec-Germany). The determination of 25-OH Vitamin D2/D3 is based on competitive Enzyme Linked Immunosorbent Assay (ELISA). Serum 25(OH) D levels of <12 ng/ml was defined as deficient, 12-20ng/ml as insufficient and >20ng/ml as sufficient Vitamin D.

#### Statistical analysis:

Data collected and analyzed by computer program SPSS" Ver. 21" Chicago. USA. Data expressed as mean, Standard deviation and number, percentage. ANOVA test Chi. Square was used to determine significance for categorical variable. Person's correlation to determine significance between variables in same group.

## Results

This study included 88 participant, 66 patients suffering from depression (their age ranged from 18-50 years (37 were females and 29 were males) and 22 healthy individuals as control their age ranged from 22-51 years (15 females and 7 males). There were no statistically significant difference regarding age and sex (Table 1). There was also no statistically significant difference according kidney function, liver function, total calcium and phosphorus. In patients group there were 31.8% of patients had mild depression, 34.8% had moderate depression and 33.3% had severe depression (Table 2).

There was statistically very high significant decrease in Vitamin D level in patients group compared to control group ( $p < 0.000$ ) (Table (3) and Fig. (1).

Table (1): Age and sex of patients and control groups.

Item	Patients group n=66	Control group n=22	p-value
<b>1- Age: Years:</b>			
Range	(18.0-50.0)	(22.0-51.0)	<i>p</i> =0.91
Mean ± SD	33.1±13.0	32.8±6.7	n.s
<b>2- Sex:</b>			
Female	37 (56.1%)	15 (68.2%)	<i>p</i> =0.22
Male	29 (43.9%)	7 (31.8%)	n.s

Table (2): Distribution of levels of depression in patients group.

Item	Levels of depression		
	Mild n=21	Moderate n=23	Severe n=22
Percentage	31.8%	34.8%	33.3%
BDI score	17-31	26-40	43-61

Table (3): Vitamin D in patients and control groups.

Item	Control group n=22	Patients group n=66	p-value
<b>Vitamin D: ng/ml:</b>			
Range	(20.60-42.50)	(5.0-39.4)	<i>p</i> <0.000***
Mean ± SD	26.86±5.81	15.12±7.50	

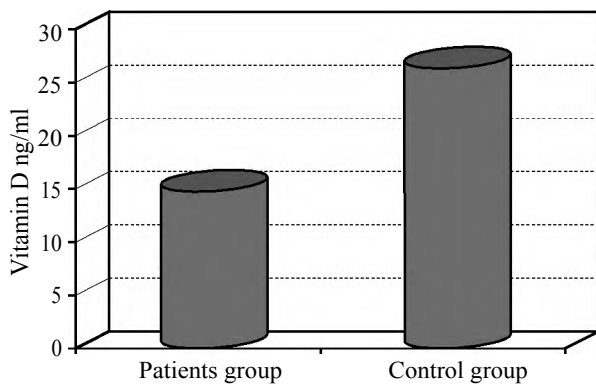


Fig. (1): Vitamin D in patients and control groups.

Table (4) illustrated distribution of Vitamin D levels in patients group, 40.9% of patients had Vitamin D deficiency (serum 25(OH)D<12ng/mL), 33.3% had Vitamin D insufficiency (serum 25(OH)D ranged from 12 to 20ng/mL), and 25.8% had sufficient level of Vitamin D (serum 25(OH)D>20 ng/mL). Table (5) illustrated range and mean values of serum Vitamin D in females and males patient groups with different levels of Vitamin D. The mean value of Vitamin D in female patients was decreased than male patients, this decrease was statistically significant (*p*<0.01). This decrease was also statistically significant in sufficient group of Vitamin D (*p*<0.001). Female patients showed insignificant decrease of Vitamin D level in both

deficient and insufficient groups of Vitamin D levels (*p*=0.40, *p*=0.30) respectively.

Table (4): Distribution of Vitamin D in patients group.

Item	Patients group
<b>Vitamin D:</b>	
Deficient: <12ng/ml	27 (40.9%)
Insufficient: 12-20ng/ml	22 (33.3%)
Sufficient: >20ng/ml	17 (25.8%)

Table (5): Vitamin D levels in females and males patients groups.

Item	Females n=37	Males n=29	p-value
<b>Vitamin D: ng/ml:</b>			
Range	5-23.9	5-39.4	
Mean ± SD	13.40±5.53	17.85±8.82	<i>p</i> <0.01 *
<b>Deficient: &lt;12ng/ml:</b>			
Range	(5.0-11.3)	(5.0-11.4)	
Mean ± SD	8.73±2.85	9.42±4.22	<i>p</i> =0.40ns
<b>Insufficient: 12-20ng/ml:</b>			
Range	(12.0-18.8)	(12.5-19.1)	
Mean ± SD	15.45±2.35	16.05±2.29	<i>p</i> =0.30ns
<b>Sufficient: &gt;20ng/ml:</b>			
Range	(20.3-24.0)	(20.4-39.4)	
Mean ± SD	22.02±1.78	26.13±6.70	<i>p</i> <0.001 **

Table (6) and Fig. (2) illustrated serum Vitamin D and levels of depression in patients group. There was statistically high significant difference between the three groups (*p*<0.000). There was statistically significant decrease of Vitamin D level in patients with moderate and severe level of depression compared to patients with mild depression (*p*1<0.000, *p*2<0.000) respectively, and also there was statistically significant decrease of Vitamin D level in patients with severe depression compared to patients with moderate depression (*p*3<0.000).

Table (6): Serum Vitamin D and levels of depression in patients group.

Item	Levels of depression			p-value
	Mild n=21	Moderate n=23	Severe n=22	
<b>Vitamin D:</b>				
<b>ng/ml:</b>				
Range	(12.0-39.4)	(5.4-20.9)	(5.0-18.8)	<i>p</i> 2<0.000***
Mean ± SD	22.33±7.19	13.69±4.11	9.73±4.60	<i>p</i> 3<0.000***

p1: Moderate versus mild.  
p2: Severe versus mild.  
p3: Severe versus moderate.

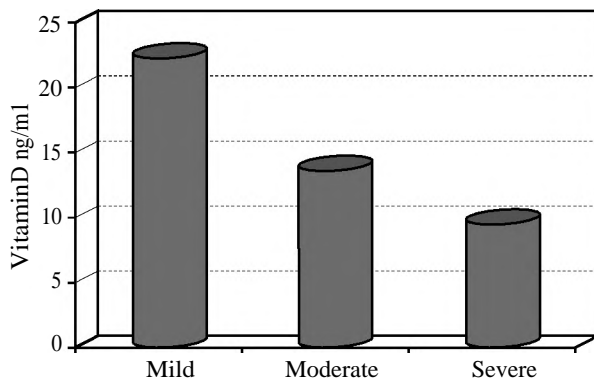


Fig. (2): Serum Vitamin D and levels of depression in patients group.

Correlation between Vitamin D and BDI score in patients group illustrated in Fig. (3). There was statistically significant negative correlation ( $r = -.784, p < 0.000$ ) between BDI score and Vitamin D in patients group Fig. (3).

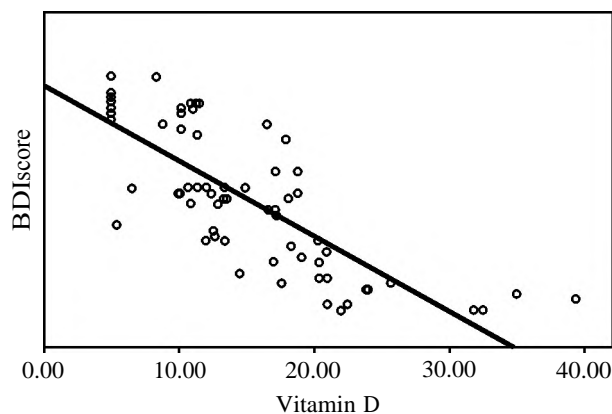


Fig. (3): Correlation between Vitamin D and BDI score in patients group.

### Discussion

Depression is associated with significant disability, mortality and healthcare costs. It is the third leading cause of disability in high-income countries and affects approximately 840 million people worldwide. Although biological, psychological and environmental theories have been advanced, the underlying pathophysiology of depression remains unknown and it is probable that several different mechanisms are involved [10].

Vitamin D is involved in numerous brain processes which include neuroimmuno modulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development [11], making it biologically plausible that this vitamin might be associated with depression [12].

Vitamin D deficiency has received increasing attention over the last decade, recently an interest

in the potential role of Vitamin D in mental health has increased, and it has been suggested that depression is dependent on Vitamin D status. Vitamin D receptors are widely distributed in areas of the human brain that are involved in depression [13]. Vitamin D helps the brain produce serotonin, a neurotransmitter critical to emotional health [14].

This study was designed to determine Vitamin D level in patients who have depression and correlate Vitamin D concentrations in serum with the severity of depression.

In this study the patients group included 66 patients, 37 (56.1%) of them were females and 29 (43.9%) of them were males. Hildebrandt et al., [15] found that the gender ratio was 2.3:1 (female: male). In a study by Dana-Alamdari et al. [8], they reported that the patients group included 44 personnel, 35 (79.5%) were females and 9 (20.5%) were males. Also Von Känel et al., [16] investigated 380 depressed patients with mean age  $47 \pm 12$  years, 70% of them were women).

This appearance of gender variation in depression may be attributed to biological factors (e.g., genetics, neurotransmitters, and hormones) and victimization (e.g., childhood trauma, restrictive gender roles [17].

In the current study 18.2% of patients with age group from 18-21 years old and 81.8% of patients with age group from 22-60 years old, this means that depression is most common among older adults. In a study done by Hussein et al., [14] on 50 Egyptian depressed females, they found that depression also affect older adults. This is also in agreement with Tsopelas et al., [18] who reported that depression is the most common mental illness in older adults, with concomitant effects on morbidity, mortality, and quality of life.

In the present study, the mean value of Vitamin D showed statistically high significant decrease in patients group when compared to control group. In the cohort study of Milaneschi et al., [19] which included older persons suggested that hypovitaminosis D is a risk factor for development of depressive symptoms. Also Jaddou et al., [6] in a national population-based household sample of 4,002 Jordanian participants, demonstrated a significant association between depression and low serum 25(OH) D level.

Kjaergaard et al., [20] evaluated Vitamin D deficiency and depression in a general population, and established that low serum 25-(OH)D levels were a significant predictor of depression. Also

Milaneschi et al., [21] reported in a case control study included 1892 patients with history of current and remitted depression and 494 healthy subjects as a controls of age group from 18-65 years old. They found that low levels of 25(OH)D were associated to presence and severity of depressive disorders.

In another study done by Jorde et al., [22] found that a low serum 25-hydroxyvitamin D level is associated with development of depression. Von Känel et al., [16] found that Vitamin D deficiency was significantly associated with increased levels of depressive symptoms in patients hospitalized with a depressive episode.

Some authors have found that high-dose Vitamin D supplementation has a distinctive effect on depressive symptoms [23,24].

The role of Vitamin D in the development of depression can be explained by that Vitamin D Receptor (VDR) and Vitamin D activating enzyme, 1-alpha-hydroxylase, are widely distributed in human brain, particularly in the hypothalamus and also in the limbic system, which is assumed to be involved in pathophysiology of the depression [25]. One area where VDR and hydroxylases have been found is the amygdala, which is the center of the limbic system, where behavior and emotions are regulated [26].

Vitamin D stimulates the expression of nerve growth factor and promotes neuritogenesis [27]. Several studies have shown that Vitamin D is involved in brain development and that its deficiency results in altered morphology (enlarged ventricles and reduced cortical thickness as it occurs in schizophrenia) and behavior in adulthood [28]. Moreover, it has been shown that Vitamin D regulates gene expression of tyrosine hydroxylase, an essential enzyme involved in the synthesis of norepinephrine and dopamine, both neurotransmitters are involved in mood regulation and depression

The immunomodulatory activity of Vitamin D has been related to inflammation that play a causal role in depression: Vitamin D has been shown to down-regulate inflammatory mediators, such as nuclear factor  $\kappa$ B, which have been linked to sickness behavior, psychosocial stress, and depression [30].

In contrast to our findings Dana-Alamdari et al., [8] in a study done on Tabriz, Iran, they reported that Vitamin D deficiency was observed in 75% of depressed patients and 80.5% of healthy subjects with no statistically significant difference. This

may be explained by that in this locality, there is limited exposure to UV due to lifestyle preferences, work schedule, and the fear of skin damage, skin-covering clothes and sunscreens are effective barriers for adequate exposure to UV rays, which impedes production of Vitamin D in the skin. Hence, intake of Vitamin D from fortified food sources to achieve adequate levels of Vitamin D appear to be necessary [8].

There are a number of possible reasons for the conflicting results among studies, including differences in population groups (i.e., ethnic and other cultural differences), age of the participants surveyed, measures of depression obtained, type of assay used for the analysis of serum Vitamin D, and statistical adjustment of known confounding factors including sun exposure [7]. Importantly, in a study by Nanri and colleagues (2009), the authors found an association between 25(OH)D and depression symptoms during winter, but not in summer or overall, thereby suggesting the season of study has a major influence on results [31].

In the current study, in patients group there was 27 patients (40.9%) had Vitamin D deficiency, 22 patients (33.3%) had Vitamin D insufficiency and 17 patients (25.8%) had sufficient level of Vitamin D. This is in consistent with a study by Hussein et al., [14] that was done on 50 Egyptian depressed females, they found (38%) of patients had Vitamin D deficiency, (46%) had Vitamin D insufficiency and (16%) had sufficient level of Vitamin D. The 25(OH)D levels was measured on a Chemiluminescence Analyzer which uses a 1-step assay [14].

Ganji et al., [27] found that in a study composed of 7970 depressed patients, Vitamin D deficiency (Vitamin D <20ng/ml) present in 24.7% of patients, Vitamin D insufficiency, (Vitamin D ranged from 20-30ng/ml) present in 29.6% of patients, Vitamin D sufficiency (Vitamin D >30ng/ml) present in 45.7% of patients. However the large number of the study sample and the type of kit they used for Vitamin D analysis which was Radioimmunoassay (RIA) kit may be the cause of some differences in the results.

Also Von Känel et al., [16], they reported that Vitamin D deficiency were present in 55.5% of patients, Vitamin D insufficiency were present in 31.8% of patients and Vitamin D sufficiency were present in 12.6% of patients. The number of patients were 380 and they used two types of kits, the first was by certified commercial laboratories using liquid chromatography-mass spectrometry, and the second was an enzyme-linked fluorescent assay.

In the current study, the mean value of Vitamin D in female patients showed statistically significant decrease when compared to male patients. This is in agreement with Hoogendijk et al., [32], and Ganji et al., [27], who have found lower levels of Vitamin D in women.

Sex differences in the relationship between 25(OH)D and depression could be attributable to different factors. This may be due to lack of sun exposure and veiled clothing style in developing countries females [33] or may be due to prolonged breast feeding without Vitamin D supplementation in the Middle East [34]. In our study, weaker association between 25(OH)D and depression in men could be due to the smaller number of men with low levels of 25(OH)D.

In the current study there was an association between lower 25(OH)D concentration and higher depression status with the lowest level of Vitamin D in severe level of depression and highest level in mild level of depression. This is in agreement with Hussein et al., [14] who reported that lower Vitamin D level was associated with more severe depression and as the level of Vitamin D level increase, not only associated with mild depression but also associated with a decreased risk for current depression and increased Vitamin D consumption elevates mood and promotes a positive outlook with statistical significant negative correlation between low Vitamin D and severity grading of depression [14].

Ganji et al., [27], found an association between lower 25(OH)D concentration and higher depression status and depression severity among a group of participants aged 15-39 years. In their study, depression status was assessed using the Diagnostic Interview Schedule (DIS) developed by the National Institute of Mental Health.

In contrast to our findings, Zhao et al., [35] utilizing the data reported in National Health and Nutritional Examination Survey (NHANES), found no significant association between serum concentrations of Vitamin D and the presence of major depression, minor depression, and moderate to severe depression. Pan et al., [36] also reported no significant association between Vitamin D status and depression in Chinese in older patients aged from 50-70 years.

In the current study, there was negative correlation between Beck Depression Inventory (BDI-II) score and Vitamin D level ( $r=-.784$ ,  $p=0.000$ ), as highest scores are associated with lowest levels of Vitamin D. This is in agreement with Lee et al.,

[37], in a study conducted on 432 men with depression using BDI score to evaluate the level of depression, they found that serum 25(OH)D levels were inversely associated with the BDI-II score ( $r=0.19$ ,  $p<0.001$ ).

Also Sang-Hyun et al., [13], reported in their study that there was a significant negative correlation between the serum 25-OHD levels and the BDI-II score. In a study by Jorde et al., [23], found that those with insufficient 25(OH)D level had significantly higher total BDI scores than those with sufficient 25(OH)D.

There are other studies using different scales to evaluate the level of depression. In a study done by Hoang et al., [38], and Hoogendijk et al., [32], they found that depression severity as measured by continuous Center for Epidemiologic Studies Depression Scale Score (CES-D) score was significantly associated with decreased 25(OH)D.

Also Polak et al., [7] found that serum 25(OH)D status was significantly negatively associated with the total CES-D scores. The study showed that for every one standard deviation increase in serum 25(OH)D (27nmol/L or 10.8ng/ml), there was a 4.5 point decrease in the CES-D score among participants aged 17-25 years.

#### Conclusions:

The present study found evidence of an association between low 25(OH)D, a marker of Vitamin D status, and depression, suggesting a direct effect of Vitamin D on development of depression. There was an association between low Vitamin D status and the severity of depression. Vitamin D deficiency was more pronounced in female patients than male patients.

#### Disclosure of conflict of interest:

The authors state that they have no conflict of interest.

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## مستوى فيتامين د في مرضى الإكتئاب

إشتملت الدراسة على ٦٦ مريضا يعانون من مرض الإكتئاب (٣٩ من الإناث و٢٧ من الذكور) تتراوح أعمارهم ما بين ١٨-٥٠ سنة، وقد قسمت حدة المرض باستخدام مقياس BDI-II إلى ثلاث مجموعات (٢١ مريض يعانون من إكتئاب طفيف، ٢٣ مريض يعانون من إكتئاب متوسط، ٢٢ مريض يعانون من إكتئاب شديد) وتضمنت الدراسة ٢٢ من الأشخاص الأصحاء كمجموعة ضابطة (١٥ من الإناث و٧ من الذكور) تتراوح أعمارهم ما بين ٢٤-٥١ وقد تم تجميع عينات من المرضى من العيادات الخارجية ووحدة الأمراض النفسية بمستشفيات جامعة أسيوط في الفترة من يونيو ٢٠١٥ إلى يناير ٢٠١٦.

وتم عمل الآتي لكل من المرضى والأشخاص الأصحاء:

- التاريخ المرضي.
- الفحص الإكلينيكي.
- الفحوصات المعملية:
- وظائف الكلى.
- وظائف كبد كاملة.
- مستوى الكالسيوم، والفوسفور.
- مستوى فيتامين (د).

الإستنتاج: وأظهرت نتائج الدراسة المعملية أن مرضى الإكتئاب يعانون من نقص ذي دلالة إحصائية في مستوى فيتامين (د) بمقارنتهم بالمجموعة الضابطة. وقد وجد نقص ذو دلالة إحصائية في مستوى فيتامين (د) في الإناث بمقارنتهم بالذكور. وقد وجد أيضا إختلاف ذو دلالة إحصائية في نسبة توزيع نقص فيتامين (د) ما بين الذكور والإناث حيث كانت نسبة الإناث ٤٥.٩٪ والإناث والذكور ٣١٪. وقد أوضحت النتائج أن في المجموعة ذات المستوى الغير كافي لفيتامين (د) كانت نسبة الإناث ٣٧.٨٪ ونسبة الذكور ٣١٪. وفي المجموعة ذات المستوى الكافي لفيتامين (د) كانت نسبة الإناث ١٦.٢٪ ونسبة الذكور ٣٧.٩٪ وهذا الإختلاف ذو دلالة إحصائية واضحة.

كان هناك إختلاف ذو دلالة إحصائية بين المجموعات الثلاث من الإكتئاب (الطفيف، المتوسط والشديد) حيث أن أقل مستوى لفيتامين (د) وجد في مجموعة المرضى الذين يعانون من الإكتئاب الشديد. وقد وجد أيضا أن هناك علاقة عكسية ذات دلالة إحصائية بين درجات الإكتئاب بمقياس BDI-II ومستوى فيتامين د في الدم حيث أنه كلما زادت درجة الإكتئاب كلما قل مستوى فيتامين د. وقد وجدت هذه العلاقة العكسية أيضا عندما تم تقسيم المرضى إلى مجموعات على حسب النوع والسن. وتبين أن نتائجنا تدعم النتائج السابقة، مما يشير إلى التأثير المباشر للفيتامين د في تطوير الإكتئاب.