Prediction of Vitamin D and Serotonin levels with increased risk Depressive in Adolescent Students

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Abstract. Vitamin D deficiency (Vt.D) is common in adolescents and is influenced by some factors, including puberty. It impacted serotonin levels, thus increasing the risk of depression. This study was conducted to assess the association between vitamin D deficiency and depression and its effect on adolescent students. A cross-sectional study of 130 adolescent students aged 12-18 years, between November 2023 to February 2024. This study investigated serum Vt.D, serotonin levels, and hematological indices such as (RBC, Hb, MCV, and MCH, of adolescents, in addition, it was dependent on the Beck Depression Inventory to calculate scales of depression. 130 adolescent students were enrolled aged 12-18, mean ± SD: 14.85±2.19. The results indicated that 77(59.2%) students had depression symptoms, median (IQR) of scores16(13_21.5), and 53(40.8%) adolescents with non-depressed (scores 5(2.5_7), who were considered as the control group, a statistically significant between these groups (p=0.035). Depression was significantly more prevalent in females 46(59.7%) than males 31(40.3%), p=0.014. Deficiency Vt.D was found in 63.6% of the total depressive adolescents and was significantly more than non-depressive adolescents 3.8%, p<0.0001, with (B: 3.199, OR: 24.5, 95%CI: 5.96 -100.74). Serum Vt.D level was significantly decreased in depressive adolescent median (IQR) 18.8(13.1_28.9) ng/ml, compared with non-depressed 52.22(42.2_62.4), (p< 0.0001), and its lowest in a type of severe depression 10.74±3.52. The depressive adolescent group had significantly lower serotonin levels in deficiency Vt.D status than non-depressive groups (143.39±60.91 vs. 314.05±46.11), p = 0.001). Correlations and linear regression analysis to predict the risk factors for depression scores showed a significant negative correlation with levels of Vt.D (r=0.786, B: -0.109, 95%CI: -0.15 to -0.065, p<0.0001), and serotonin (r=0.848, B: 0.003, 95%CI: -0.032 to -0.019, p<0.0001), respectively. Deficiency Vt.D is an important risk factor for adolescents, especially in females, and is associated with an increased risk of depression in adolescent students

1 Introduction

Vitamin D, a steroid hormone, is generated in the body by UVB radiation on the skin or ingested orally through food and supplements. It has been shown to protect against a variety

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of immune system disorders [1]. In addition, it is a micronutrient and an endogenous metabolite acting as a hormone, binding to the vitamin D receptor (VDR) present in many organs and tissues [2], and it is which exerts a crucial role in the maintenance of bone and calcium homeostasis [3]. Vitamin D insufficiency is common worldwide and has been related to a higher risk of depression [4]. Furthermore, a fat-soluble vitamin, is also classified as a hormone due to its ability to be synthesized in the body and the similarity of its mechanism of action to steroid hormones, and it is important for maintaining normal physiological functions as well as body growth and development. Vitamin D deficiency has been linked to several pathological conditions, while high levels can be toxic [5].Vitamin D has two forms: ergocalciferol (D2) and cholecalciferol (D3). it is recommended to increase vitamin D intake and get enough sunlight to keep serum 25-hydroxyvitamin D at least at 30 ng/mL (75 nmol/L) and preferably at 40-60 ng/mL (100-150 nmol/L) to get the most out of vitamin D [6]. Vitamin D supplementation in foods or the use of vitamin D supplements are current ways of increasing vitamin D levels and treating deficiency [7]. Serotonin (5-HT) is a vital neurotransmitter in the central nervous system as well as a regulatory hormone that regulates a wide variety of physiological functions. Perhaps the most classically defined roles of 5-HT are central to mood, sleep, and anxiety management and peripheral to gastrointestinal motility modulation [8]. However, 5-HT has recently been recognized as an important metabolic hormone that contributes to glucose homeostasis and obesity, with a causal association between circulating 5-HT levels and metabolic disorders (9). Serotonergic agents are still frequently used to treat a variety of mental health issues (10). The aim of this study: The study assessed the relationship between Vitamin D deficiency and Its effect On depression and cases of nervous irritability, which most adolescents currently suffer from, which affects their social behavior. To achieve this goal, we can measure the hormone serotonin and create a questionnaire specifically for the axes of depression and then present it to a psychiatrist...to link clinical results to laboratory results Clinically and To determine whether depression and vitamin D deficiency or insufficiency are related.

2 Materials and Methods

This sectional study was performed with one hundred and thirty (130) adolescents (males and females) with ages ranging from (12-18) years, Samples were collected from different areas in the center and districts of Al-Najaf al-Ashraf City, Iraq. It was conducted from the first of November 2023 to the end of January 2024. Based on the study's experimental design and the formal data for every participant, The participants were healthy, all samples suffering from incurable diseases, cancer patients, tumors, endocrine disorders, mental and physical disabilities, and deaf and mute patients were excluded. The adolescents answered a questionnaire that included the Beck Depression Inventory to determine the degree of depression for each adolescent. Five ml of venous blood samples were obtained for hematological and biochemical screening tests. The collected blood was divided into almost (2ml) and put in an EDTA tube (ethylene diamine tetra acetic acid), while the other part (3ml) was put in gel tubes for separates of serum, centrifuged at 3000 rpm for 5 minutes to completely separate the serum which preserved in new Eppendorf tubes and stored at -20 °C until the measurement hormones (25 (OH) Vt.D Serotonin) by ELISA according kit that supply from (Bioassay technology laboratory company).

All data were statistically analyzed by IBM SPSS 26 (SPSS Inc., Chicago, IL). Nominal data was reported by frequencies and percentages with the use of the chi-square test. The normal distribution used the Kolmogorov-Smirnov test. Numerical data were expressed as mean ± standard deviation (SD), an independent t-test between two groups, an ANOVA test and post hoc for comparison among groups. Median (IQR) interquartile range for

continuous variables with non-normal, distribution and Kruskal-Wallis test for among groups. Pearson's or Spearman Rho coefficient correlation tests between serum levels Vt.D and Serotonin with depressive scores. Linear and logistic nominal regression analyses were performed to predict the of risk depression. The significant level was considered as p-value <0.05.

3 Results

3.1 Distribution of Demographic variables in adolescent students

The statistical analysis in Table (1) indicated that 130 adolescent students were enrolled aged 12-18, with mean ± SD: 14.85±2.19. The results indicated to significant increase (p=0.035) in number and percentage 77(59.2%) students had depression symptom median (IQR) of scores about 16(13_21.5), and 53(40.8%) adolescents with non-depressed (scores 5(2.5_7), who considered as controls group, a statistically significant in depressed scores (p<0.001). No significant differences in depressive students with early adolescence 37 (48.1%) as compared with late adolescence students 40 (51.9%), p= 0. 921. The study included 64(49.2%) males and 66 (50.8%) females of total adolescent students; Significant increases were observed in depressed females 46 (59.7%) more than males 31 (40.3%) p=0.014.

A significant (p<0.001) increase in mean BMI of depressive adolescents (23.3±4.3 kg/m^2), when compared with (20.21±4.39 kg/m^2). While, BMI categories showed depressive adolescents with underweight (20.8%), less than non-depressive (41.5%), but groups with normal weight (50.6%), overweight and obesity about (19.5%), and (9.1%), depressed highest than non-depressive-adolescents-about (45.3%), (7.5%), and (5.7%), respectively, with significant differences p=0.039. The Education level was involved 80(61.5%) in Middle Grade of which 47(61.0%) depressive,33(62.3%) non-depressive while in Secondary Grade 50 (38.5%) from which 30(39.0%) depressive, 20(37.7%) non-depressive, no significant differences were observed (p=0.888). A significant decrease (p=0.017) was observed in adolescent students who took Vt. D Supplement about 22(16.9%), had depressive symptoms 8(10.4%), and 14(26.4%) non-depressive, as compared with total students 108(83.1%) who don't take Vt. D Supplement about 69(89.6%) with depressive, and 39(73.6%) who non-depressive. According to Vt.D_ Status, depressive adolescents had deficiency Vt.D 49(63.6%) and Insufficiency Vt. D 15(19.5%) more than non-depressed students 2(3.8%), and 5(9.4%), but who with Sufficiency VtD about 13(16.9%) depressive, lowest 46(86.8%) in non-depressive groups, these results showed a significant difference (p<0.001). As well the Beck depression scale the results indicated that depressive adolescents who had a simple type the scores were 35(26.9%), mild was 25(19.2%), and with severe depression was 17(13.1%), from these results, it was confirmed that there is a significant difference (p=0.042).

Table. 1. Distribution of All Studied Categories in Adolescent Students.

Variables	Categories	Total	Depressive	Non-Depressive	X^2 p-value
Studied samples		130 (100%)	77 (59.2%)	53 (40.8%)	4.431 0.035*
Depression Scores	**Mean ± SD** **Median (IQR)**	12.51±7.96 11.5(6.75-18)	17.69±5.97 16(13_21.5)	4.98±2.74 5(2.5_7)	<0.001**
Age (year)	**Mean ± SD**	14.85±2.19	14.94±2.2	14.72±2.2	0.579
	Early adolescence	62 (47.7%)	37 (48.1%)	25 (47.2%)	0.010
	Late adolescence	68 (52.3%)	40 (51.9%)	28 (52.8%)	0.921

Sex	**Male**	64 (49.2%)	31(40.3%)	33 (62.3%)	6.081
	Female	66 (50.8%)	46 (59.7%)	20 (37.7%)	0.014*
BMI (kg/m^2)	**Mean ± SD**		23.3±4.3	20.21±4.39	<0.001**
	Underweight **Normal weight** **Overweight** **Obesity**	38 (29.2%) 63 (48.5%) 19 (14.6%) 10 (7.7%)	16 (20.8%) 39 (50.6%) 15 (19.5%) 7 (9.1%)	22 (41.5%) 24 (45.3%) 4 (7.5%) 3 (5.7%)	8.341 0.039*
Education level	**Middle Grade**	80 (61.5%)	47 (61.0%)	33 (62.3%)	0.020
	Secondary Grade	50 (38.5%)	30 (39.0%)	20 (37.7%)	0.888
Vt.D Supplement	**Yes**	22 (16.9%)	8 (10.4%)	14 (26.4%)	5.734
	No	108 (83.1%)	69 (89.6%)	39 (73.6%)	0.017*
Vt. D Status	**Deficiency**	51 (39.2%)	49 (63.6%)	2 (3.8%)	64.540
	Insufficiency	20 (15.4%)	15 (19.5%)	5 (9.4%)	<0.001**
	Sufficiency	59 (45.4%)	13 (16.9%)	46 (86.8%)	
Types of Depressives	**Non**	53 (40.8%)	0	53 (100%)	
	Simple	35 (26.9%)	35(45.5%)	0	6.338
	Mild	25 (19.2%)	25 (32.5%)	0	0.042*
	Severe	17 (13.1%)	17 (22.1%)	0	

*Significant differences at p-value *, **<0.05, <0.01. X^2: Chi-Square test.*

3.2 Association of Serotonin and 25 (OH) Vt.D levels with depression in adolescent students

The statistical analysis in Table 2, showed that depressed adolescents have significant (p<0.001) decreases in levels of 25 (OH) Vt.D (ng/mL), (Mean: 22.3, median (IQR): 18.8(13.1_28.9), and Serotonin (pg/mL) (Mean: 180.52; median (IQR): 174.6(115.5_241.7), as compared with non-depressed (Mean:50.54; median (IQR): 52.22(42.2_62.4), and 390.6; 360.31(308.7_482.9), respectively. Serum levels of Vt.D (ng/mL), explained a significant decrease in 17 adolescents with severe and 25 mild depressive means of about 10.74±3.52, and 16.95±5.41 lowest in 35 with simple depressive 31.77±13.53, p<0.001, figure 1. In a similar finding, Serum levels of Serotonin (pg/mL), noted a significant decrease in adolescents with severe and mild depressive mean of about 88.49±20.29, and 253.16±49.88, lower than adolescents with simple depressive 253.16±49.88, p<0.001, figure 2.

Depressive adolescents with Vt.D Deficiency have significant (p<0001) lower mean Serotonin levels about 143.39±60.91 than adolescents with Insufficiency Vt.D 229.09±79.96, and Sufficiency Vt.D 264.48±35.61 to compare with 314.05±46.11, 344.17±99.82, and 398.98±119.52, in non- depressive groups respectively. Figure 3.

Table 2. Serotonin and 25 (OH) Vt.D levels associated with depression in adolescent students.

Adolescent Students	**25 (OH) Vt.D (ng/mL)**		**Serotonin (pg/mL)**		**p-value**
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	
Depressive	22.32±13.21	18.8(13.1_28.9)	180.52±79.25	174.6(115.5_241.7)	<0.001**
Non-Depressive	50.54±14.85	52.22(42.2_62.4)	390.6±116.9	360.31(308.7_482.9)	<0.001**

*Significant differences at p-value *<0.5, **<0.01. median (IQR): inter quartal rang*

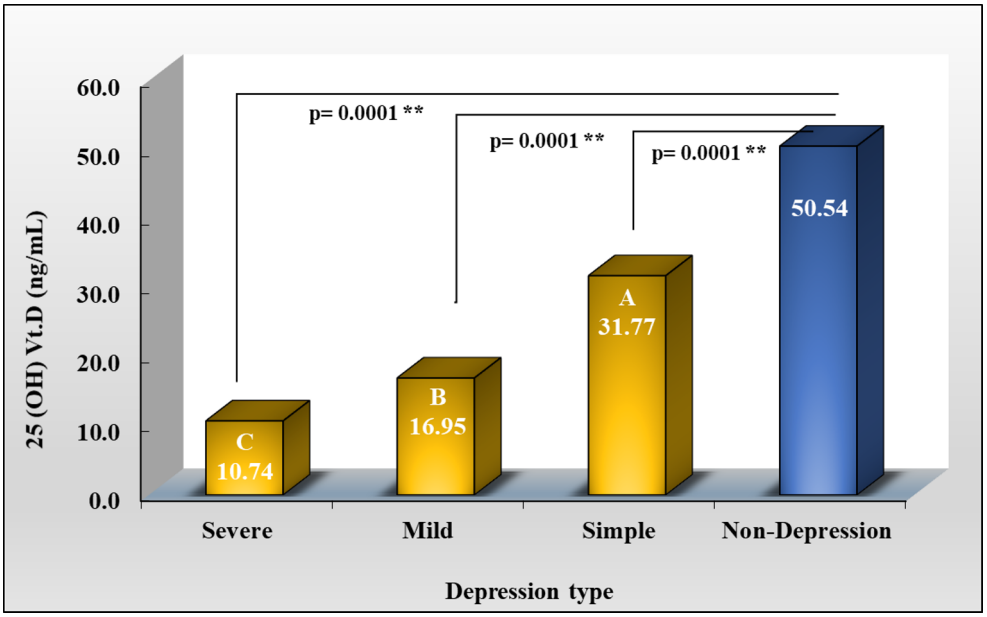

Fig. 1. Serum 25 (OH) Vt.D (ng/mL) levels in adolescent students with among types of depression. *Different letters have significant differences at ** p-value <0.01.*

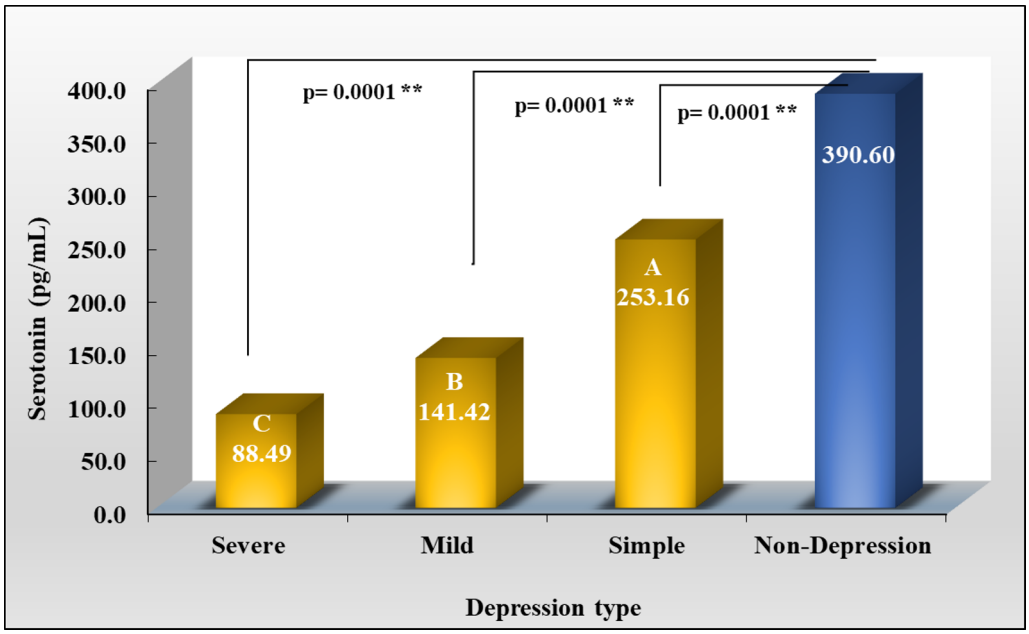

Fig. 2. Serum Serotonin (pg/mL) levels in adolescent students with among types of depression.

*Different letters significant differences at ** p-value <0.01.*

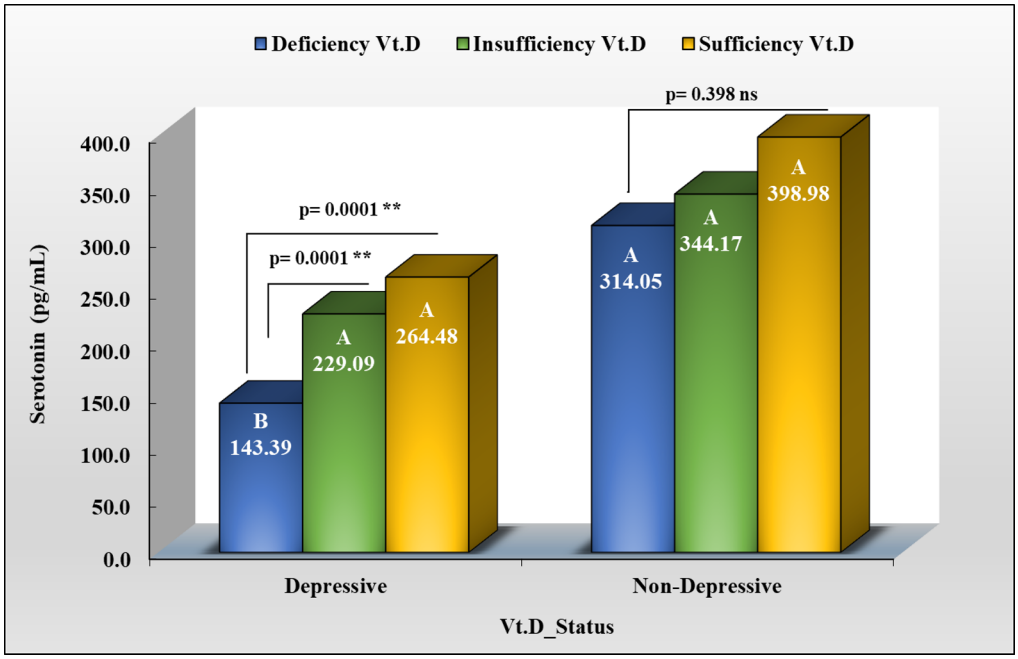

Figure 3. Serum Serotonin level (pg/ml) in adolescent students with Vt. D status.

3.3 Different letters Significant differences at p-value **<0.01, ns: non-significant

3.3.1 Effects of Vt.D Supplement on Serotonin levels

The results are in the figure. 4, indicated to comparison between 22(17%) adolescent taking Vt.D. as a nutritional supplement compared with 108(83%) adolescents who did not take Vt.D. The results revealed a statistically significant increase in mean Serotonin levels of groups with Vt.D Supplement (380.47±119.48) pg/mL; median (IQR): 368.7(254.9-481.3). in comparison to adolescents without Vt.D Supplement (242.89±134.22) pg/mL; median (IQR): 218.6 (131.5-322.9), p<0.0001.

3.3.2 Correlations and regression of depression scores with Vt.D and Serotonin levels

The results of correlations observed that depression scores were significantly negatively correlated (p<0.0001) with levels of Vt.D (r=0.786), and Serotonin (r=0.848), figures 5, and 6. but, a significant positive correlation between last the two hormones (r=0.737, p=0.0001), in adolescent students. figure 7. Linear regression analysis in Table 3. showed that depression scores were not associated with the age of adolescent students, but it was significantly related to BMI (B: 0.752; 95%CI: 0.448 to 1.056, p<0.001). Also, depression scores were reversely predicted with serum levels of 25 (OH) Vt.D (ng/mL) by effect size (B: -0.109; 95%CI: -0.15 to -0.065; p<0.001), more than Serotonin levels by effect size (B: -0.026; 95%CI: -0.032 to -0.019, p<0.002).

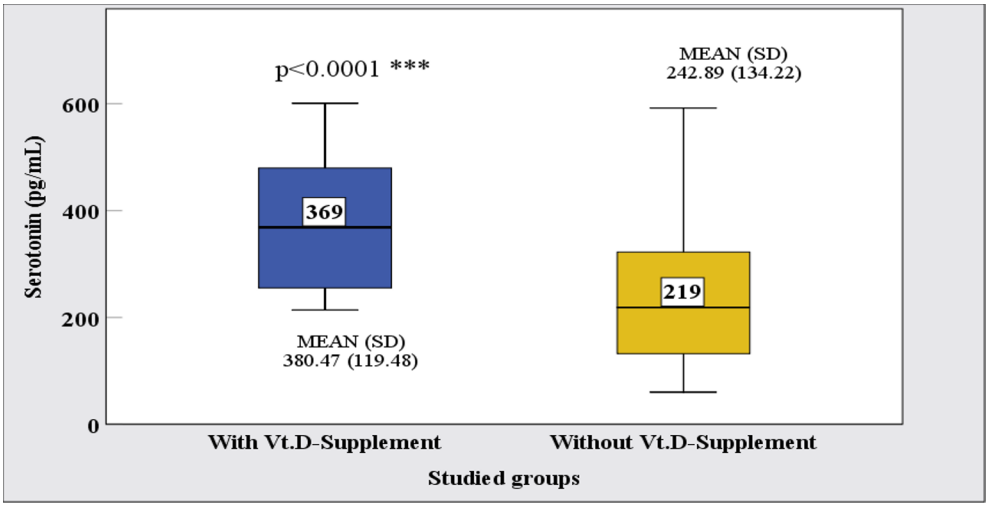

Fig. 4. Serum Serotonin level (pg/ml) in adolescent students with Vt.D supplement and without Vt.D supplement. Significant differences at p-value ***<0.001.

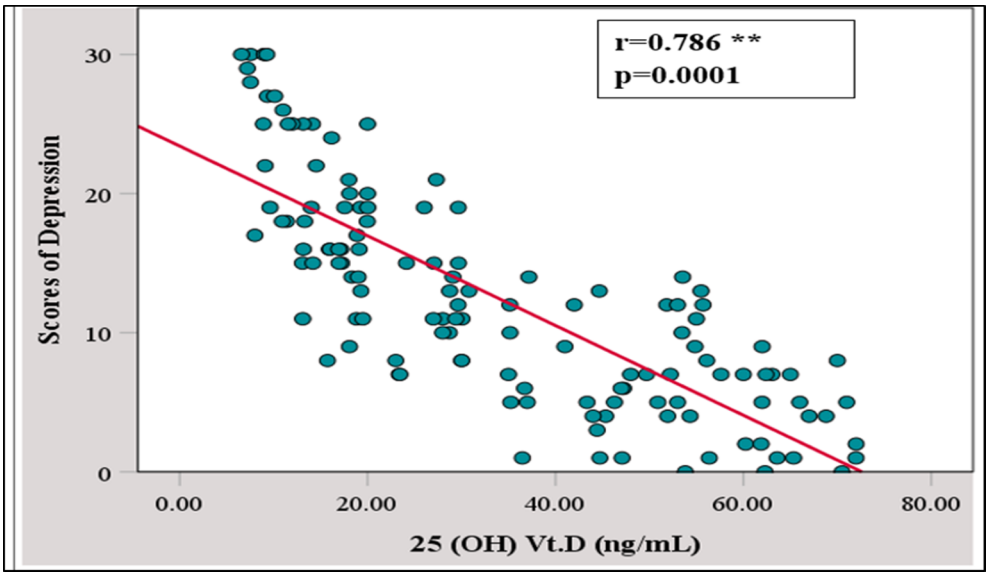

Fig. 5. Correlation of depression scores with vitamin D in adolescents.

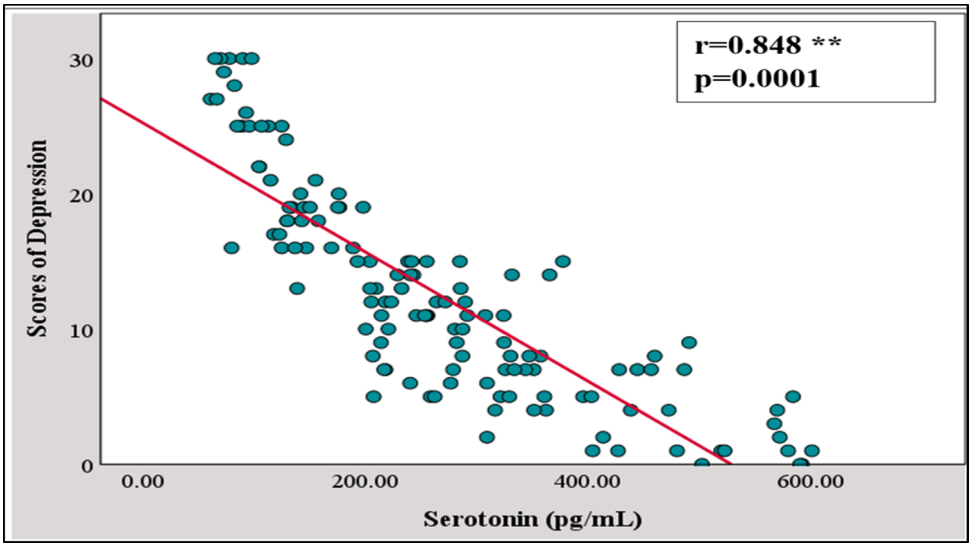

Fig. 6. Correlation of depression scores with serotonin in adolescents.

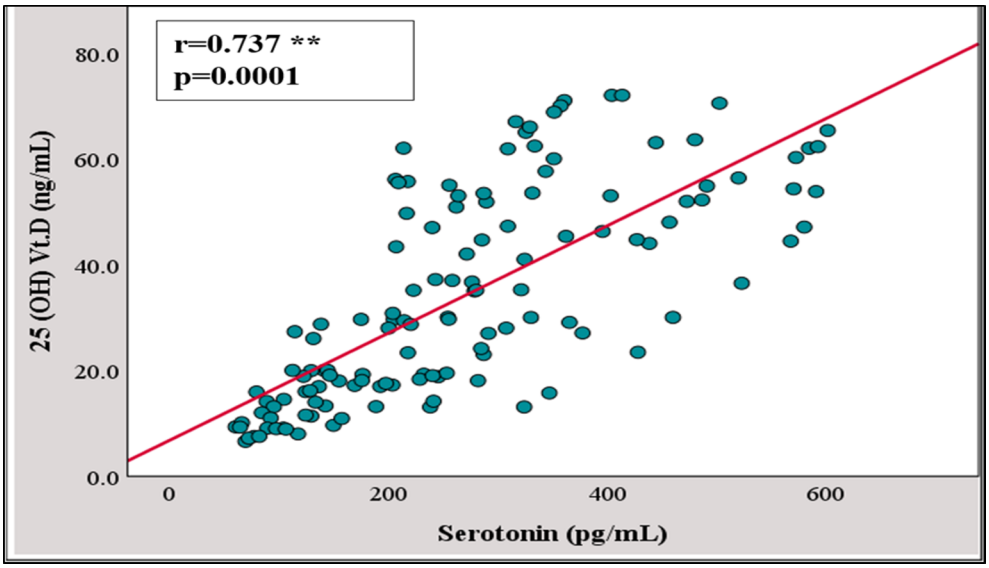

Fig. 7. Correlations of serotonin with vitamin D in adolescents.

Table 3. Linear regression to predict the independent risk factors associated with the depression scores.

Predicts parameters	B	SE	p-value	95.0% CI
Age (year)	-0.045	0.310	0.885	-0.658 to 0.568
BMI (kg/m^2)	0.752	0.154	<0.001**	0.448 to 1.056
25 (OH) Vt.D (ng/mL)	-0.109	0.022	<0.001**	-0.15 to -0.065
Serotonin (pg/mL)	-0.026	0.003	<0.002**	-0.032 to -0.019

*Significant differences at p-value **<0.01.*

B: Unstandardized Coefficients (effect size). SE: standard error. CI: Confidence Interval. Dependent Variable: Score of depression.

3.4 Nominal Regression analysis to predict the risk factors associated with depression

Nominal Regression analysis in Table 4, indicated that an increase in risk depression predicts no significance with an age of early and late adolescent students as equal by (OR: 1.480, and 1.429). The risk of depression associated with females (OR: 2.33; p=0.002), is higher than males (OR: 0.939; p=0.803). Adolescents with overweight and obese were highest predicted to be depressive (OR: 3.750, p=0.019; and OR: 2.333, p=0.022), then normal weight and underweight (OR:1.625, p=0.061; and OR: 0.727, p=0.332), respectively. No effects of education level. The risk of depression was elevated in adolescents with no Vt. D Supplement (OR: 1.769, p=004), more than those who had taken Vt. D Supplement (OR: 0.571, p=0.207). Highly predicted depression in adolescents with deficiency Vt. D (OR: 24.4, p=<0.001), as compared with insufficiency (OR: 3.00, p=0.033), but no effects in and sufficiency adolescent and (OR:0.283, p=<0.001**)**

Table 4. Nominal Regression analysis to predict the categories of risk factors associated with depression.

Predicts [a] in depressive groups		**B**	**p-value**	**OR**	**95% CI**
Age (year)	**Early adolescence**	0.392	0.130	1.480	0.891 to 2.458
	Late adolescence	0.357	0.148	1.429	0.881 to 2.315
Sex	**Male**	-0.063	0.803	0.939	0.575 to 1.534
	Female	0.833	0.002	2.300*	1.361 to 3.888
BMI classification	**Underweight**	-0.318	0.332	0.727	0.382 to 1.385
	Normal weight	0.486	0.061	1.625	0.977 to 2.702
	Overweight	1.322	0.019	3.750*	1.245 to 11.299
	Obesity	0.847	0.022	2.333	0.603 to 9.023
Education level	**Middle Grade**	0.354	0.119	1.424	0.913 to 2.223
	Secondary Grade	0.405	0.160	1.500	0.852 to 2.641
Vt. D Supplement	**Yes**	-0.560	0.207	0.571	0.240 to 1.362
	No	0.571*	0.004	1.769	1.195 to 2.620
Vt. D_ Status	**Deficiency Vt. D**	3.199	0.0001	24.50**	5.958 to 100.744
	Insufficiency Vt. D	1.099	0.033	3.00 *	1.090 to 8.254
	Sufficiency Vt. D	-1.264	<0.001	0.283**	0.153 to 0.523

*Significant differences at p-value *<0.05, **<0.01. a: The category references are non-depressive. 95% Confidence Interval for OR*

4 Discussion

The study indicated in Table (1) that the largest percentage 77(59.2%) of the study sample (adolescent students) are depressed and 53(40.8%) adolescents with a non-depressed and significant increase (p=0.035). 34% of adolescents worldwide, between the ages of 10 and 19, are at risk of developing clinical depression [11]. Furthermore, adolescence and early adulthood are key periods for growth and development [12]. the study showed Significant increases were observed in depressed females 46 (59.7%) more than males 31 (40.3%) p=0.014. Adolescents are more susceptible to psychological problems during the formative and turbulent adolescent years due to changes in their bodies, minds, and social interactions. Girls have roughly twice the prevalence of depression as boys after pubertal onset [13]. The results in the same table indicate the presence of significant differences

between the four BMI classes and depression, with underweight persons not showing greater values than normal weight or overweight individuals. Obese individuals had greater depression scores compared to those with other BMI classifications. Furthermore, underweight did not influence depression as compared to normal weight. Adolescents with overweight and obese were predicted to be depressive When compared with normal weight and underweight, in other words, Depressive symptoms have a positive correlation with BMI [14]. Numerous studies have demonstrated a bidirectional relationship between obesity and depression, with the presence of one raising the likelihood of the other. Moreover, there are compelling arguments for the theory that these illnesses are linked together in a vicious cycle that amplifies one another's negative physiological responses [15] Research indicates that those with depression have a 58% higher risk of becoming obese [16]. The results showed No effects of education level were observed (p=0.888). The results showed that Adolescents who take vitamin D as a dietary supplement had fewer depression symptoms about 22(16.9%), had depressive symptoms 8(10.4%), and 14(26.4%) non-depressives, as compared with a total student 108(83.1%) who don't take Vt. D Supplement about 69(89.6%) with depressive, and 39(73.6%) who non-depressive. Vitamin D supplementation may ameliorate clinical depression [17]. Another study on the therapeutic effect of vitamin D supplementation also yields intriguing results. In this study, vitamin D supplementation was given for three months to a group of patients suffering from major depressive disorder (a severe form of depression). The Beck Depression Inventory (BDI) scale was used in this study to assess the impact of vitamin D. Following vitamin D treatment, the BDI scores of females with moderate, severe, and intense depression were significantly reduced ($P<0.05$). In males, only the group with severe depression showed a significant improvement in the BDI score ($P<0.05$) (107) [18]. Low vitamin D levels in the body can be brought on by some variables, including age, gender, race or ethnicity, skin color, season, illness, and usage of vitamin D supplements, [19]. The study indicated that the highest percentage of depressed adolescent students are those who suffer from a deficiency in vitamin D According to Vt. D_ Status. Because it regulates neurotransmission and provides neuroprotection. Vitamin D insufficiency may cause inactivated receptors and may result in depression [20]. This study found a statistically significant difference in vitamin D levels between males and females, with females being more deficient. Females may have higher body fat levels, spend more time indoors, and wear clothing that covers the majority of their body. Children and teenagers frequently suffer from vitamin D deficiency, which can be attributed to many conditions including obesity and puberty. Another risk factor for vitamin D insufficiency is puberty, particularly in girls and obese kids. It is crucial to monitor vitamin D levels in these age groups due to the increased risk and the fact that childhood and adolescence are the most critical periods for developing a healthy skeleton [21]. Previous evidence suggests that vitamin D insufficiency may increase the risk of depression [22]. The results of the study were also shown in Table (2) Depression has a negative relationship with vitamin D and serotonin. Depression may result from low serotonin levels, which are influenced by low vitamin D levels [23]. Vitamin D affects serotonin synthesis by a unique biological mechanism [24]. Serotonin is always involved in the pathophysiology of depression [25]. Vitamin D modulates the levels of 5-HT, DA, and NE receptors in the brain. Low vitamin D levels can lead to depression by reducing these neurotransmitters [26]. Vitamin D insufficiency can disrupt 5-HT synthesis, leading to abnormal neuron growth in the brain and serotonergic system. 5-HT affects the hippocampus, where it promotes neuronal growth and synaptic plasticity, which may contribute to depression onset and therapy. It also implies that vitamin D deprivation can affect dopaminergic neuron development and have serious consequences on the formation of depression. Hence, Vitamin D can affect monoamine levels and contribute to depression [27]. According to the monoamine hypothesis, one of the established pathways linked to the

onset of depression is a 5-HT shortage [28]. Depression has long been recognized to be a heterogeneous disorder from a pharmacotherapeutic standpoint as well as from a genetic, clinical, and biological one. Only a subgroup of depressed individuals exhibits decreased serotonin activity, which is unquestionably crucial to the pathophysiology of depression. The statistical analysis in Table 2, showed that positive correlation between and serotonin in adolescent students Neuroprotection and neurotransmission modulation are aided by vitamin D. Thus, depression may arise from a vitamin D deficit due to inactivated receptors [29].

5 Conclusion

Because of the negative correlation between vitamin D and depression, thus deficiency Vt. D is an important risk factor for adolescents and was associated with lower serotonin levels, especially in females, and increased risk of depression. Vitamin D deficiency can be made up for by management of taking supplements to help those who suffer from depression.

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