ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 02, pp.47176-47181, February, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

EFFECT OF VITAMIN D3 ON IMPROVEMENT OF PATIENTS AGED 18-65 WITH TREATMENT RESISTANT DEPRESSION (TRD)

[1]Mohammad Effatpanah, [2]Alireza Mahjoub, [3]Maryam Kia, [4]Mojtaba Sedaghat, [5]Parisa Fazlipanah, [6]Hamidreza Hekmat and *,[7]Zohreh Asgari

[1]Associate Professor, M.D. Child and Adolescent Psychiatrist, Tehran University of Medical Sciences, Tehran, Iran
[2]General Practitioners, Students Research Center of International Campus, Tehran University of Medical Sciences, Tehran, Iran
[3]M.D. Internal Specialist, Tehran University of Medical Sciences, Tehran, Iran
[4]Associate Professor, Ph.D. Epidemiologist, Tehran University of Medical Sciences, Tehran, Iran
[5]M.D. Anesthesiologist, Students Research Center of International Campus, Tehran University of Medical Sciences, Tehran, Iran
[6]Associate Professor, M.D. Cardiologist, Tehran University of Medical Sciences, Tehran, Iran
[7]Medical Student, Students Research Center of International Campus, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received 23rd November, 2016
Received in revised form
16th December, 2016
Accepted 20th January, 2017
Published online 28th February, 2017

Key words:
Depression,
vitamin D,
Calcium,
Phosphorous,
Parathyroid hormone.

ABSTRACT

The aim of this study was to investigate the effect of vitamin D3in response to the treatment ofstage1treatment-resistant depression. In this clinical trial, 64 patients with treatment-resistant depression in the age range 18-65yearsreferred to Ziaeian Hospital were enrolled. Patients were randomly divided into two groups of 32 patients in each group and in addition to the main treatment for depression, in group A, vitamin D was administered and group B, received placebo of vitamin D. There were no statistically significant differences in the levels of alkaline phosphatise and phosphorus in group A and B before and after taking vitamin D or placebo. The parathyroid hormone inpatients receiving vitamin D were reduced, although this reduction was not statistically significant. The average level of vitamin Din patients taking these vitamins significantly increased. The results of this study showed that patients who had received vitamin D, their depression were quite improved and while the average depression score of patients receiving placebo was moderate at the end of the study. Since depression is accompanied by decreased serum level of vitamin D, consumption of supplementary vitamin D can be helpful in the treatment of these patients.

Citation: Mohammad Effatpanah, Alireza Mahjoub, Maryam Kia, Mojtaba Sedaghat, Parisa Fazlipanah, Hamidreza Hekmat and Zohreh Asgari, 2017. "Effect of vitamin d3 on improvement of patients aged 18-65 with treatment resistant depression (TRD)", *International Journal of Current Research*, 9, (02), 47176-47181.

INTRODUCTION

Major depressive disorder is a type of mood disorder which described as a period of major depression without any manic history for at least two weeks in the present of low mood, lack of interest and lack of pleasure from normal activities of life. Also fear of the symptoms such as lack of experiencing pleasure, lack of energy, change in appetite and sleep patterns, fidget and sluggishness, reduced concentration, indecisiveness, suicidal idea, feelings of guilt and worthlessness must be present during the depression period (Bromet *et al*., 2011).

Corresponding author: Zohreh Asgari,
Medical Student, Students Research Center of International Campus, Tehran University of Medical Sciences, Tehran, Iran

Treatment-Resistant Depression (TRD) refers to depression with insufficient clinical response to the current treatment with antidepressants (Keller, 2004; Thase, 2003).

TRD is divided into five stages:

- Stage 1: failure in adequate treatment with themajor class of antidepressants.
- Stage 2: stage one plus failure in response to another class of antidepressants.
- Stage 3: stage two plus failure in response to treatment with lithium.

- Stage 4: stage three plus failure in response to treatment with Monoamine-oxidase inhibitor (MAOI).
- Stage 5: stage four plus failure in response to treatment with Electroconvulsive Therapy (ECT) (Cowen, 1998).

Despite the essential role of vitamin D in human health and survival, vitamin D deficiency as a considerable health problem is propounded in whole world (Mithal *et al*., 2009). Decreased serum level of vitamin D which is lower than 50nmol/L could be a sign of vitamin D deficiency. Serum levels less than a 25nmol / literare classified as sever deficiency and serum level of 25-75 nmol/liter is classified as moderate deficiency (Holick *et al*., 2005). Vitamin D from the diet or dermal synthesis from sunlight is biologically inactive; this inactive form undergoes two enzymatic hydroxylation reactions in order to convert to calcitriol (1, 25-dihydroxycholecalciferol), the biologically active form of vitamin D. Metabolites and other analogues of this compound are also referred to as Vitamin D. Several studies have emphasized the role of vitamin D in prevention of diseases including heart diseases, malignancy, intestinal inflammatory diseases, multiple sclerosis, Rheumatoid arthritis, diabetes type 1, autoimmune diseases and infectious diseases (Maghbooli *et al*., 2007; Institute of Medicine, Food and Nutrition Board, 2010). Also, some in vitro studies have shown that vitamin D can have a suppressant effect on cytokines, including interleukin-2,6,12,Tumor Necrosis Factor-alpha (TNF-α), TNF-β and interferon-γ (Vitamin D, 2008; Gloth *et al*., 1999; Chiu *et al*., 2004; Borissova *et al*., 2003). Vitamin D increases the intestinal absorbance of phosphorus and calcium, decreases the execration of these substances from kidneys and improves bone density (Deluca, 2004; Aris *et al*., 2005; Hoecker and Kanegaye, 2002). In clinical studies, low serum level of vitamin D is reported to be accompanied by psychiatric symptoms such as stress, depression and decline in cognitive functions (Holick, 2007; Przybelski and Binkley, 2007; Wilkins *et al*., 2006; Armstrong *et al*., 2007). Observation of the reduced serum level of parathyroid hormone (PTH) amongst psychiatric patients can be important, because the parathyroid receptors are found in the brain and a high level of parathyroid hormone is then associated with dysfunction of central nervous system (Weaver *et al*., 1995; Smogorzewski, 2001). Presence of several reports regarding the reduced serum level of vitamin D in different psychiatric disorders upsurges the attraction and complexity of this topic (Schneider *et al*., 2000). Vitamin D is known to be associated with the manifestation of seasonal affective disorder symptoms (Schlager *et al*., 1993). Serum level of vitamin D is reduced because of the reduction of sunlight in winter; symptoms of seasonal depression can be improved by prescribing vitamin D supplement in some cases (Gloth *et al*., 1999; Lansdowne and Provost, 1998). Association of reduced serum level of vitamin D with depression and positive effect of vitamin D supplement may be a sign of the presence of causality, at least in one of the depression types such as seasonal depression (Jorde *et al*., 2008). According to the results, depression was associated with reduced serum level of vitamin D ($p<0.001$) and increased serum level of parathyroid hormone ($p=0.01$), but there was no statistically significant difference observed among patients with depression and healthy cases, according to serum calcium level ($p=0.69$) and serum phosphorus level ($p=0.15$) (Jamilian *et al*., 2012). In a study by Mozaffari-Khosravi *et al*. (2013), 120 patients with using self-report rating method of Beck Depression Inventory (BDI-II)and vitamin D deficiency were divided into 3 groups: vitamin D IU 300.000 was used for group 1 via Intramuscular injection (IM), vitamin D IU 150.000 was used for group 2 and group 3 was the control group. Evaluation of the results obtained from BDI-II indicated the presence of a significant difference amongst group 1 and 3 (Mozaffari-Khosravi, 2013).

In a study by Kjargaard *et al*. (2012), participants with low serum levels of vitamin D had more depressive symptoms compared to those with normal serum levels of vitamin D using the Montgomery–Asberg Depression Rating Scale (MADRS). The patients with low serum levels of vitamin D were divided into 2 groups: group 1 patients were received vitamin D_3 IU 40.000 per week for a period of six weeks and group 2 patients were received placebo. In this study, vitamin D_3 supplement did not show a significant effect on improving depressive symptoms (Kjargaard, 2012). According to the research, serum level of vitamin D lower than 50nmol/l (or < 20 ng/ml) is classified as vitamin D deficiency and a serum level greater than this amount is sufficient for suppression of PTH (Saliba, 2011). In a study by Jorde *et al*. (2008), participants with lower than 40 nmol/l, serum level of vitamin D, had more depressive symptoms using BDI-II compared to those with normal serum levelof vitamin D; and prescribing vitamin D_3supplement was led to a significant improvement on the BDI-II results after one year (Jorde, 2008). Therefore, regarding to the stated evidence and absence of such a study in our country, this study was carried out with the aim of evaluation of serum level of vitamin D in patients with treatment-resistant depression (TRD). Without any doubt, a better clarifying of the pathophysiology of this disorder could be a way to discover new treatment methods for patients with TRD.

MATERIALS AND METHODS

In this clinical trial, 64 patients with stage 1 TRD aged 18-65 who admitted to Psychiatric Center of Ziyayian Hospital were included after obtaining informed consent. Diagnosis of TRD was confirmed by a psychiatrist through interviewing the patients considering Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Serum level of 25-hydroxy vitamin D, calcium, phosphorus, alkaline phosphatase and parathyroid hormone were measured in all patients. The severity of the patient's depression was rated by using the Hamilton Depression Rating Scale (HDRS).

Inclusion criteria were: patients with major depressive disorder (MDD) who received a maximum dose of Sertraline which is a selective serotonin reuptake inhibitor (SSRI) class for a period of at least 4-6 weeks and showed no response to this medicine. Serum level of vitamin D in all participants were lower than 50 nmol/L (or < 20ng/ml).

Exclusion criteria were: sarcoidosis, tuberculosis, malignancy, hypercalcaemia, renal insufficiency (e.g. nephrolithiasis), digestive problems like in celiac disease, pregnancy and breast feeding.

All fertile women were examined for β-Human chorionic gonadotropin (β-hCG)-negative, and they were usedan adequate contraceptive method during the study. Then patients with stage 1 TRD and serum vitamin D level lower than 50 nmol/L (or < 20ng/ml) were randomly selected; block randomization in blocks of four is used for this purpose. The participants were divided into two equal groups of 32 participants. Each group were continued to receive a maximum dose of sertraline. Then group A, in addition to sertraline

received bupropion 450mg daily for a period of 3 months, an oral weekly dose of vitamin D_3IU 50000 for 8 weeks plus 1 month dose of vitamin D_3 IU 50000 for a period of 4 months (12 oral dose of vitamin D_3 IU 50000 in total) and calcium carbonate 500mg twice daily for a period of 3 months. Group B, in addition to sertraline received bupropion 450mg daily for a period of 3 months, oral weekly vitamin D_3 placebo tablets for 8 weeks plus 1 monthly vitamin D_3 placebo tablet for a period of 4 months (12 placebo tablets of vitamin D_3 in total) and calcium carbonate 500mg twice daily for a period of 3 months. During this period, the project assistant was reminding patients to take their medication by telephone. Diagnosis of TRD was confirmed by a psychiatrist through interviewing the patients considering Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Serum level of 25-hydroxy vitamin D, calcium, PTH, phosphorus and alkaline phosphatase were measured and the severity of the patient's depression was rated again by HDRS questionnaire again after 3 months and the results from group A was compared with group B (placebo group). This was a double-blind study in which neither the experimenter who was responsible for rating the severity of depression via HDRS questionnaire nor the participants know who is receiving vitamin D3 supplement or placebo.

Assessment tools used in this study

HDRS questionnaire was used in order to evaluate the severity of the patient's depression. This questionnaire has been widely used in clinical practice and become a standard in clinical trials in Iran. HDRS questionnaire evaluates the different dimensions of depression (behavioural, physical, cognitive, emotional, feelings of guilt, hypochondria, sexual, somatic symptoms, suicide ideation and insomnia).Based on the HDRS, score of (17-24)was classified as mild depression; scores of(25-30) was classified as moderate depression and score of (≥31) was classified as severe depression. HDRS questionnaire was translated into Farsi by Mahyar and Mousavi-nasab in1986 and has been used in different clinical research (Gharaei *et al*., 2000). The patients were divided into group-A, who received vitamin D_3 supplement and group-B who received placebo. SPSS-21 software was used in order to analyse and evaluate the collected data and laboratory information. Some measures such as mean, standard deviation (SD), dispersion, frequency and percentage were used to describe the data and required tables and graphs were plotted. The quantitative variables were described as Mean and SD; and the qualitative variables were described as a percentage. Paired sample T-test was used in order to compare the mean values.

RESULTS

Four of the participants were male (6.25%) and sixty of them were female (93.75). The mean age of patients was 36.93±9.36; the youngest patient was aged 21 and the oldest one was aged 62. The mean age of patients in group A was 38.06±9.35 and in group B was 35.74±9.38. The mean of alkaline phosphatase level in group A before and after receiving vitamin D_3 supplement were 125.64 and 134.44 respectively and there was no statistically significant difference (P=0.54). Besides, the mean of alkaline phosphatase level in group B before and after receiving placebo were 114.23 and 117 respectively and therefore there was no statistically significant difference (P=0.97) (table1). According to the illustrated results in table 1, a statistically significant difference was observed for the mean of calcium level in group A before and after receiving vitamin D_3 (8.62 and 9.56 respectively; P=0.02). However, as it was expected, no significant difference was reached for the mean of calcium level in group B who received placebo (p=0.08). The mean of phosphorus level in group A before and after receiving vitamin D_3 were 3.98 and 4.50 respectively and in group B at the start of the study and after completion were 3.32 and 3.95 respectively. According to the obtained results from this study, no statistically significant difference regarding the phosphorus level was observed in group A (p=0.73) and group B (p=0.06) (Table 1). PTH level in patients who received vitamin D_3, was not statistically significant (p=0.91). Likewise, in placebo group, no statistically significant difference was observed regarding PTH level (p=0.65) (Table 1).

According to the obtained results from the present study, the mean of vitamin D level in patients who received vitamin D_3 was significantly increased (p=0.0001). The mean of vitamin Dwas increased from 9.10 (before administration of vitamin D_3) to 34.2 (after administration of vitamin D_3). The serum level of vitamin D in patients who received placebo at the beginning of the study was 9.46 and it was reached to 10.14 at the end of the study (p=0.01) (Table 1).

Table 1. Alkaline phosphatase and calcium level in group A and B

	Groups		Mean	Standard deviation	Minimum	Maximum	P value
Alkaline phosphatase	A	Before	125.64	47.5	70	268	0.54
		After	134.44	19.39	100	160	
	B	Before	114.23	25.19	70	166	0.97
		After	117	21.79	90	150	
Calcium	A	Before	8.62	0.82	7	9.5	0.02
		After	9.56	0.5	8.8	10.3	
	B	Before	8.97	0.73	7	10	0.08
		After	9.46	0.62	8	11	
Phosphorus	A	Before	3.98	0.95	2.5	5.7	0.73
		After	4.5	0.65	3.8	5.9	
	B	Before	3.32	0.65	2	4.8	0.06
		After	3.95	1.14	2.5	9	
PTH	A	Before	87.54	24.75	36	137	0.91
		After	88.19	20.64	42	109	
	B	Before	104.2	67.23	38	297	0.65
		After	97.66	24.53	44	40	
Vitamin D	A	Before	9.1	3.73	3.5	19.7	0.0001
		After	34.2	11.8	5	73	
	B	Before	9.46	4.1	3.1	17.9	0.01
		After	10.14	3.94	3	18	

Depression severity score in patients of both groups A and B

According to the obtained results from the evaluation, it was determined that the depression score of patients who received vitamin D_3 was completely improved while the depression score of patients who received placebo was still within the score range for moderate depression (Table 2).

Table 2. Depression severity score in all participants

Groups		Mean	Standard deviation	Minimum	Maximum	P value
A	before	26.81	3.86	20	35	0.0001
	after	13.84	3.7	6	24	
B	before	27.41	4.5	19	42	0.001
	after	23.9	5.28	16	42	

DISCUSSION

Depression is a common mental disorder which is concomitant with a high degree of chronicity, diversity of symptoms, high risk of recurrence, physical and mental impairments. Prevalence of the disease in public population is approximately 25% and the risk of recurrence is higher than 50% (Kalpan and Sadock, 2002; Kaplan and Sadock, 2000). Studies have shown that nearly 20% of the patients referring to outpatient clinics suffer from depression. Generally, depression is a common word used for mood disorders such as major depressive disorder (the most severe type of depression), dysthymia and bipolar depression. Depression is a major cause of disability in the world (Gelenberg and Hopkins, 2007). MDD is considered as one of the main public health problems with a lifetime prevalence rate of 15%to 20% (Bhatia and Bhatia, 2007). By the year 2020, MDD is estimated to become the second most common disease after coronary artery disease in the world (Kessler *et al*., 2005). Depression affects the patient's body, mood and behavior and represents with symptoms such as: persistent feelings of sadness, anger, helplessness or hopelessness, loss of interest in activities previously enjoyed, chronic fatigue, cognitive problems, suicide and suicidal thoughts. Structure, severity and duration of symptoms of mood disorders are different. In addition, depression affects the academic performance and communication with other people and is the leading cause of suicide (Gelder *et al*., 2001). Mood changing is the constant and persistent symptoms which may continue for days, weeks and months (Baune *et al*., 2010). Apart from the depressed mood, the patients with major depression have also several cognitive problems which are probably linked to dysfunction of the frontal lobe;despite the recovery of depression, these problems remain and result in poor performance of the patients (Gruber *et al*., 2007; Stordal *et al*., 2004). Evidences show that the patient's cognitive function is deteriorated with each depression relapse (Hosseini and Mahdizadeh, 2011). Among 64 patients assessed in this study, 4 patients (6.25%) were male and others (60 patients, 93.75%) were female. The current estimates show that MDD affects twice as many women as men. Biological, hormonal, life cycle and psychosocial factors related to women is linked to a higher prevalence rate of depression in women. Researchers have shown that hormones directly affect the brain, which controls one's affections, emotions and mood. For instance, women are especially prone to depression after pregnancy. Many women experience a short period of sorrow and sadness after pregnancy, but this may progress into severe postpartum depression in some women. In more serious situations, initiating a treatment and emotional support for mothers is essential. Many women have to deal with excessive stress at work and during domestic chores. However, this matter has remained uncertain that why some women struggle to overcome great challenges in their life which may lead to an increased risk of depression while others seems to meet the same challenges with confidence without developing risk of depression (Gawęda and Kokoszka, 2014).

In the present study, the mean age of patients with major depression was 36.93±9.36; the youngest patient was aged 21 and the oldest one was aged 62. Many resources have stated that the disease is most common in those who are 25-44 years of age (Kalpan and Sadock, 2002; Kaplan and Sadock, 2000). According to the obtained results from the present study, no statistically significant difference regarding the alkaline phosphatase level (p=0.54; p=0.97) and phosphorus level (p=0.06; p=0.73) were observed in group A and B. In addition, the mean of calcium level in patients who received vitamin D_3 (group A), was significantly increased after receiving vitamin D_3 (P=0.02). However, as it was expected, no significant difference was reached for the mean of calcium level in group B who received placebo (p=0.08). In the present study, PTH level in patients who received vitamin D_3 was reduced, but this was not statistically significant (p=0.91). Likewise, in placebo group, no statistically significant difference was observed regarding the PTH level (p=0.65). The mean of vitamin D level in patients who received vitamin D_3 was significantly increased (p=0.0001). The mean of vitamin D in group A was significantly increased from 9.10 (before administration of vitamin D_3) to 34.2 (after administration of vitamin D_3); but there was no significant increase regarding the serum level of vitamin D in patients who received placebo (group B). Nevertheless the increased level of vitamin D in group B was statistically significant (p=0.01) but the level of vitamin D was still within the deficient range. According to the obtained results of the evaluation, it was determined that the depression score of patients who received vitamin D_3 was completely improved while the depression score of patients who received placebo was still within the score range for moderate depression. According to the obtained findings from the present study, depression was concomitant with reduced serum level of vitamin D; and using vitamin D_3 supplement had a significant effect on improving depression in patients. In a study which was carried out in Amsterdam on 1282 patients aged 65-69 with depression, the serum level of vitamin D in these patients was lower than healthy individuals; the PTH was higher than normal ranges. In the Amsterdam study, the calcium and phosphorus level were not evaluated in particular. However, this study declared that autoradiograph and immunohistochemistry were shown that target tissue of 25-hydroxy vitamin D is most dependent to exocrine, endocrine secretion and somatotropin processes rather than calcium level alone (Hoogendijk *et al*., 2008). In a study which was carried out at Frankfurt University on 110 participants, including patients with major depressive disorder and healthy individuals, level of vitamin D, calcium and phosphorus were evaluated. Only the vitamin D level in patients was significantly lower than the control group and this corresponds with our study (Schneider *et al*., 2000). A double-blinded, randomized clinical trial at the University of Tromso in Norway evaluated the effect of vitamin D supplement for depression symptoms amongst overweight or obese patients. This study was carried out on 441 obese patients with depression and demonstrated that there was a link between serum level of vitamin D and depression symptoms. The results from this study correspond with our study (Jorde *et al*., 2008).

In a cross-sectional study in 2005, the vitamin D level of 3262 individuals aged 50-70 from Shanghai and Beijing in China were evaluated. This study concluded that there was no link between vitamin D level and depression symptoms in Chinese middle-aged and elderly. As this was a cross-sectional study and the causal relation between vitamin D level and depression was uncertain, it was suggested that further studies were needed in order to determine the causal relation between vitamin D and depression (Pan *et al*., 2009).

Conclusion

As depression is associated with reduced serum level of vitamin D, using vitamin D_3 supplement could be an

appropriate way in treating these patients. However, undertaking clinical trials regarding the effect of vitamin D_3 supplement in treating depressed patients are suggested for further studies.

REFERENCES

Aris RM, Merkel PA, Bachrach LK. 2005. Guide to bone health and disease in cystic fibrosis. *I Clin Endocrinol Metab*., 90:1888-96.

Armstrong DJ, Meenagh GK, Bickle I, Lee AS, Curran ES, Finch MB. 2007. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol*., 26(4): 551-4.

Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, Mitchell D. 2010. The role of cognitive impairment in general functioning in major depression. *Psychiatry Res*., 176(2-3): 183-189.

Bhatia SK, Bhatia SC. 2007. Childhood and adolescent depression. *Am Fam Physician*, 75(1): 73-80.

Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. 2003. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract*., 57:258-61.

Bromet E, Andrade LH, Hwang I. 2011. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine*, 9:90.

Chiu KC, Chu A, Go VL, Saad MF. 2004. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr*., 79:820-825.

Cowen PJ. 1998. Pharmacological management of treatment-resistant-depression. *Advances in Psychiatric treatment*, 4:320.327.

Deluca HF. 2004. Overview of general physiologic features and functions of vitamin D. *Am I clin Nutr*., 80: suppl:16895-16965.

Gawęda L. and Kokoszka A. 2014. Meta-cognitive beliefs as a mediator for the relationship between Cloninger's temperament and character dimensions and depressive and anxiety symptoms among healthy subjects. *Comprehensive Psychiatry*, 55;1029–1037.

Gelder M, Gath D and Mayou R. 2001. Oxford text book of psychiatry, London: Oxford, 11: 269-325، 16: 457- 490.

Gelenberg AJ, Hopkins HS. 2007. Assessing and treating depression in primary care medicine. *Am J Med*., 120(2): 105-108.

Gharaei B, Mehryar AH, Mehrabi M. 2000. Attribution style in patients with anxiety and depression comorbidity. *Iran J Psychiatry Clin Psychol*., 5(20): 437-442.

Gloth FM, Alam W, Hollis B. 1999. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging*., 3 (1):5-7.

Gloth FM, Alam W, Hollis B. 1999. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging*., 3(1):5-7.

Gruber S, Rathgeber K, Braunig P, Gauggel S. 2007. Stability and course of neuropsychological deficits in manic and depressed bipolar patients compared to patients with major depression. *J Affect Disord*., 104(1-3): 61-71.

Hoecker CC. and Kanegaye JT. 2002. Recurrent febrile seizures, anusual presentation of nutritional rickets. *The Journal of Emergency Medicine*, 23(4):367-370.

Holick MF, Siris ES, Binkley N. 2005. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab*., 90:3215-3224.

Holick MF. 2007. Vitamin D deficiency. *N Engl J Med*., 357(3):266-81.

Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. 2008. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry*, 65(5):508-12.

Hosseini SM, Mahdizadeh AA. 2011. Depression and its factors. *Researcher Journal*, 8: 106-115.

Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

Jamilian HR, Bagherzadeh K, Nazeri Z. 2012. Comparison of the serum levels of vitamin D, parathyroid hormone, calcium, and phosphorous in individuals with major depression and schizophrenics with healthy subjects. *Arak Medical University Journal (AMUJ)*, 14(59): 19-26.

Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. 2008. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med*., 264(6):599-609.

Jorde R. 2008. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *Journal of Internal Medicine*, 599-609.

Kalpan H & Sadock, 2002. Synopsis of psychiatry 9th ed. Baltimore: Williams and Wilkins, 15: 534-590، 28: 822-843.

Kaplan H. and Sadock B. 2000. Comprehensive text book of psychiatry, Philadelphia: Lippincott Williams and wilkins. 1: 1284-1441.

Keller MB. 2004. Remission versus response: The new gold standard of antidepressant care. *Journal of Clinical Psychiatry*, 65 (suppl.4):53-54.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. 2005. Lifetime prevalence and age of -onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry*, 62(6): 593-602.

Kjargaard M. 2012. Effect of vitamin D supplement on depression score in people with low levels of serum 25-hydroxy vitamin D:nested case- control study and randomised clinical trial. *The British Journal of Psychiatry*, 201:360-368.

Lansdowne AT. and Provost SC. 1998. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl)*, 135(4): 319-23.

Maghbooli Z, Shafaei AR, Karimi F, Madani FS. 2007. Vitamin D status in mothers and their newborns in Iran. *BMC Pregnancy and Childbirth*, 7(1): p. 6.

Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J. 2009. IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int*., 20(11):1807-20 19.

Mozaffari-Khosravi H. 2013. The effect of 2 different Single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency. *Journal of Clinical Psychopharmacology*, 3:378-385.

Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X. 2009. Association between depressive symptoms and 25-

hydroxyvitamin D in middle-aged and elderly Chinese. *J Affect Disord*., 118(1-3): 240-3.

Przybelski RJ. and Binkley NC. 2007. Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. *Arch Biochem Biophys*., 460(2):202-5.

Saliba, W. 2011. The relationship between serum 25OH D and parathyroid hormon levels. *Am J Med*., 124:1165.

Schlager D, Schwartz JE, Bromet EJ. 1993. Seasonal variations of current symptoms in a healthy population. *Br J Psychiatry*, 163:322-6.

Schneider B, Weber B, Frensch A, Stein J, Fritz J. 2000. Vitamin D in schizophrenia, major depression and alcoholism. *J Neural Transm*., 107(7):839-42.

Smogorzewski MJ. 2001. Central nervous dysfunction in uremia. *Am J Kidney Dis*., 38(4 Suppl 1): S122-8.

Stordal K, Lundervold A, Egeland J, Mykletun A, Asbjornsen A, Landro N. 2004. Impairment across executive functions in recurrent major depression. *Nord J Psychiatry*, 58(1): 41-47.

Thase ME. 2003. Evaluating antidepressant therapies: remission as the optimal outcome. *Journal of Clinical Psychiatry*, 64(suppl.13):18-25.

Vitamin D" - Evidence-based monograph. Mayo Clinic. Natural Standard Research Collaboration 2008-03-01). November 2008.

Weaver DR, Deeds JD, Lee K, Segre GV. 1995. Localization of parathyroid hormone-related peptide (PTHrP) and PTH/PTHrP receptor mRNAs in rat brain. *Brain Res Mol Brain Res*., 28(2): 296-310.

Wilkins CH, Sheline YI, Roe CM, Birge SJ, Morris JC. 2006. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry*, 14(12):1032-40.

****