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ORIGINAL ARTICLE

A Study of Vitamin D Deficiency Associated with Alteration of Serum Calcium Level in Cases of Depression

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ABSTRACT

Depression is a highly prevalent and debilitating chronic illness that can be difficult to treat. Most likely, depression is caused by a combination of genetic, psychological, environmental, and biological factors. Vitamin D is a fat soluble vitamin and its actions are mediated by the vitamin D receptor(VDR) that binds the active form of vitamin D[1,25(OH)$_2$ D]. Receptors for vitamin D are present, among other locations, on neurons and glia in many areas of the brain (cingulate cortex and hippocampus, thalamus, hypothalamus, and substantia nigra), which are most likely involved in the pathophysiology of depression. Major depression was also found to be accompanied by hyperactivity of subcellular calcium signalling. The present study is conducted to know the prevalence of vitamin D deficiency in diagnosed cases of depression and its association with alteration of serum calcium level. This study is performed on a sample of 90 subjects out of which 45 are clinically diagnosed cases of depression attending the Department of Psychiatry of Gauhati Medical College and Hospital, Guwahati, who were diagnosed by psychiatrists as per the fifth edition of the Diagnostic and Statistical manual of Mental disorders(DSM-V) criteria and rest 45 were normal healthy individuals. Estimation of Vitamin D was done by immune enzymatic assay whereas serum calcium values were obtained in semi auto analyser. The results of Vitamin D and serum calcium were compared by independent t-test. Further the correlation between serum Vitamin D and serum calcium among the study groups were carried out by Pearson's correlation test. Analysis of the results reveal that mean values of serum Vitamin D is lower in case group as compared to control group while in case of calcium it is vice versa. However, in both the cases the differences in mean values were observed to be statistically significant. The current study shows that alterations in concentration of serum vitamin D and calcium may be considered to be an important factor in development and progression of depression.

Key words: *Vitamin D, Depression, Mood disorders*

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INTRODUCTION

The mood disorders encompass a variety of affective problems that include major (or unipolar) depression, bipolar disorder, cyclothymia, dysthymia and substrate induced mood disorder. The World Health Report 2001 has identified unipolar depression as the 4th cause of Disability-Adjusted Life Years (DALYs) in all ages, and the 2nd cause in the age group of 15-44 years. Depression is a highly prevalent and debilitating chronic illness that can be difficult to treat (Lopez, *et al.,* 2006; Cuijpers, *et al.,* 2012) and both depressive

disorders and sub threshold depressive symptoms are associated with significant disability, mortality, and health care costs (Broadhead, *et al.,* 1990; Pietrzak , *et al.,* 2013).

Major depression is a severe psychiatric disorder that has lifetime prevalence in excess of 15% and is the fourth leading cause of disability worldwide. A recent WHO report predicts that depression will be the leading cause of disability and premature death by 2020, second only to Ischaemic heart disease (Mental Health Regional committee for the Eastern Mediterranean Forty eight Session Riyadh, 2001). Depressive disorders are characterized by depressed mood, anhedonia, anergy, and negative self-esteem. Typical symptoms of depression also include fatigue, as well as sleep and appetite disturbances. These symptoms contribute to a decline in these patients' activity levels which can lead to decreased ultraviolet ray exposure as a result of reduced time spent outdoors leading to vitamin D deficiency.

According to the immune theory of affective disorders, excessive inflammatory activity plays an important role in the pathogenesis of depression. The initial view was that the underlying cause of depression was the excessive production of cytokines by macrophages. However, subsequent studies suggested that IL-1 and IL-6 may play key roles in the pathogenesis of depressive disorders.

Vitamin D is a fat-soluble hormone and in recent years it has been found that it is important for neuro development and for neuropsychiatric disorders (Cui, *et al.,* 2015). It passes the blood-brain barrier, and both the vitamin D receptor (VDR) and the enzyme that hydroxylates the circulating form S-25(OH)D into the active metabolite 1,25-dihydroxy-vitamin D (1,25(OH)2 D) are found in the human brain (Eyles, *et al.,* 2005). There has been proposed sex differences where low vitamin D has been found associated with negative symptoms in males, and to increased anti-social aggression in females (Cieslak, *et al.,* 2014). The strongest link between low S-25(OH)D and psychiatric symptomatology has been found in depression (Anglin, *et al.,* 2013; Milaneschi, *et al.,* 2014)

ROLE OF VITAMIN D IN DEPRESSION

The mechanism through which vitamin D plays a role in metal health is not clearly understood. Active vitamin D enhances glutathione metabolism in neurons, therefore, promotes antioxidant activities that protect them from oxidative degenerative processes (Shinpo, *et al.,* 2000; Jorde, *et al.,* 2006).

Proposed biological mechanisms for the association between vitamin D and depression include that vitamin D:

1. The role of calcitriol or 1, 25 dihydroxy cholecalciferol, the bioactive form of vitamin D, in brain tissue has been confirmed by the presence of vitamin D receptors (VDR) and hydroxylases in various brain regions (Prüfer, *et al.,* 1999).
2. The mechanism through which vitamin D plays a role in metal health is not clearly understood. Active vitamin D enhances glutathione metabolism in neurons, therefore, promotes antioxidant activities that protect them from oxidative degenerative processes. Vitamin D also stimulates the expression of nerve growth factor and promotes neuritogenesis (Brown, *et al.,* 2003).

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 behaviour in adulthood (Eyles, *et al.,* 2003; Almeras, *et al.,* 2007).

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 (Newmark and Newmark, 2007)

Low levels of 25(OH)D could be involved in the pathogenesis of depression in several ways. Moreover, the distribution of target neurons of 25(OH)D suggests an influence of

synthesis levels of nerve growth factor (Wion, *et al.,* 1991), acetylcholine acetylase, serotonin, testosterone, thyroid hormone, and tyrosine hydroxylase messenger RNA (Stumpf, 1995; Stumpf and O'Brien, 1987) which have all been implicated in the pathogenesis of depression in human beings.

ROLE OF CALCIUM IN DEPRESSION

Some studies reveal that hypercalcemia per se is known to result in psyconeurological symptoms such as depression and delirium (Petersen, 1968). A modest oral calcium lactate supplement (approximately one additional recommended daily allowance of dietary calcium) has been found to worsened depression. Salmon calcitonin, which lowers blood calcium levels, also decreased quantified motor activity, frequency and severity of periodic agitated episodes, serum creatine phosphokinase and prolactin and nocturnal sleep, while vitamin D or calcium lactate raised them (Whooley and Simon, 2000). Major depression was found to be accompanied by hyperactivity of subcellular calcium signalling, and any means of reducing pathological neuronal calcium ion flow to reduce resulting pathological nitric oxide neuronal output would have anti-depressant effect (Paul, 2001).

OBJECTIVE OF THE STUDY

1. To determine the relationship between the pathophysiology of major depressive disorder and vitamin D deficiency with alteration in serum calcium level.
2. To estimate the serum 25(OH)D levels in patients of diagnosed cases of depression and to compare the levels with normal healthy controls.
3. To study the correlation of serum 25(OH) D with serum calcium levels in cases of Depression.

MATERIALS AND METHODS

The study was carried out in the Department of Psychiatry, Gauhati medical College Hospital (GMCH), Guwahati and biochemical tests were carried out in the Department of Biochemistry, GMCH during the period of during the period of August 2017 to July 2018. The present study was approved by the Institutional Ethics Committee, Gauhati Medical College, Guwahati vide letter no. MC/190/2007/Pt-I/123, dated the 13th December 2017. Proper consent was taken before the sample collection from all the subjects/guardian of the patients after explaining to them the significance of the study and the anticipated results.

The study was conducted on 45 clinically diagnosed cases of depression patients, attending the Department of Psychiatry, who constituted the case group. Another 45 apparently healthy, age and sex matched, random individuals constituted the normal control group.

The case group consisted of 45 patients with major depression from both indoor and outdoor patients of the Department of Psychiatry of GMCH. They are diagnosed by the psychiatrists, GMCH as per the fifth edition of DSM(DSM-V) criteria.

The control group consists of 45 (Forty-five) age and sex matched healthy subjects without any psychiatric diseases. Furthermore, informed consent for participation to the study was obtained from all subjects under the control group after explaining to them the significance of the tests, the aims of the study and the anticipated results. A careful screening was done in selecting subjects so that persons having pathology referable to any system, particularly persons having history of diabetes mellitus, cardiac disease, renal disease, hypertension, tuberculosis either in the past or present was not included in this group. Female patients during pregnancy and lactation were excluded. A thorough history (Personnel, occupational etc.) & physical examination was done to exclude all these possibilities.

Biochemical analysis of serum Vitamin D and Calcium level-

- Estimation of serum Vitamin D was done by immuno enzymatic assay by using MARK/BIORAD 12134/-/- GMCH/MICRO/SERO/ER-01 ELISA READER.
- Serum calcium level was estimated by using MERCK microlab 300 semi auto-analyser.

RESULT

The age distribution in both the case (patients with depression) and control (healthy individuals) groups is shown in table 1. The age range in both the groups was 15 to 64 years. The mean age of the subjects in case group was 33.155 years with a standard deviation of (σ) of ±12.384 years.

Table 1: Comparison Table Showing Statistics of Age of Subjects in the Studied Groups

Statistics	Case	Control	Significance
N	45	45	t = 0.1192
Mean	33.1555	32.844	P = 0.9054*
S.D	± 12.384	± 12.378	
SEM	1.846	1.846	
Range	15-64	15-64	

* Unpaired t-test shows that p>0.05 and hence can be inferred that the mean of age differences of subjects in experimental group and control group is not significant.

Table 2: Age Wise Distribution of Serum 25(OH) Vitamin D in Case and Control Group

Age in years	15-24	25-34	35-44	45-54	55-64
	Mean±SD 25(OH) Vitamin D (ng/ml)				
Case Group	15.0971±7.614	13.6525±6.120	15.755±6.896	12.0122±4.889	10.36±1.471
Control Group	29.2214±8.051	33.1292±5.151	31.6425±3.996	36.9077±14.118	35.05±3.960

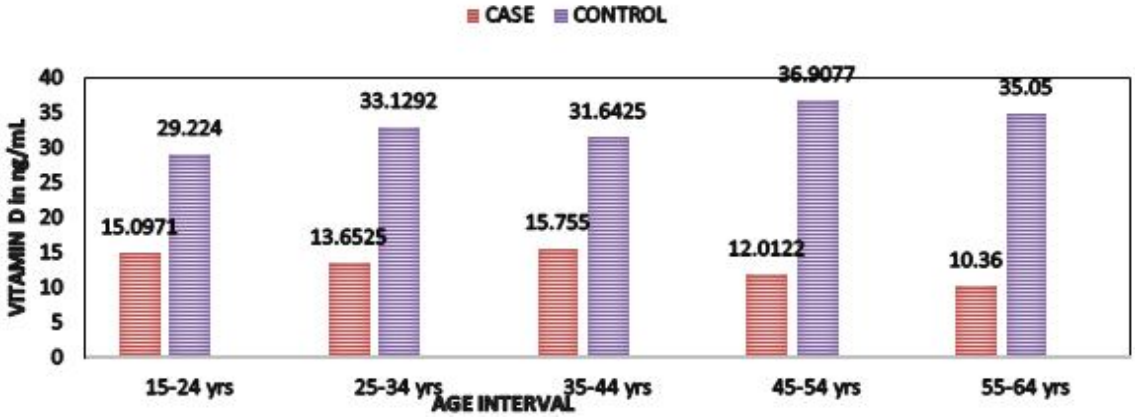

Fig. 1: Histogram showing distribution of mean serum 25(OH) Vitamin D levels in different age intervals of studied groups

Table 3: Distribution of serum 25(OH) Vitamin D in case and control group

Statistics	Case group	Control group	Significance
N	45	45	p<0.0001*
Mean	14.001	32.490	t=11.632
SEM	0.9526	1.272	
SD	± 6.390	± 8.536	
MEDIAN	12.070	31.400	

* Unpaired t-test shows p<0.05 and hence can be inferred that the difference of mean of serum 25(OH) Vitamin D levels in subjects of case and control group is extremely significant.

SERUM CALCIUM

The mean value of serum total calcium in case group was 10.1 mg/dL with a standard deviation (σ) of ± 0.7909 mg/dL and the range was between 8.6mg/dL and 11.2 mg/dL. The mean value of serum total calcium in control group was 9.762 mg/dL with a standard deviation (σ) of ± 0.3833 mg/dL.

Table 4: Frequency distribution of serum total calcium in case and control group

Class interval	Case Group		Control Group	
	Frequency	Rel. Freq.	Frequency	Rel. Freq.
8.4 to 8.9 mg/dL	6	0.1333	2	0.0444
9.0 to 9.5 mg/dL	5	0.1111	10	0.2222
9.6 to 10.1 mg/dL	12	0.2666	27	0.6
10.2 to 10.7 mg/dL	10	0.2222	6	0.1333
10.8 to 11.3 mg/dL	12	0.2666	Nil	0

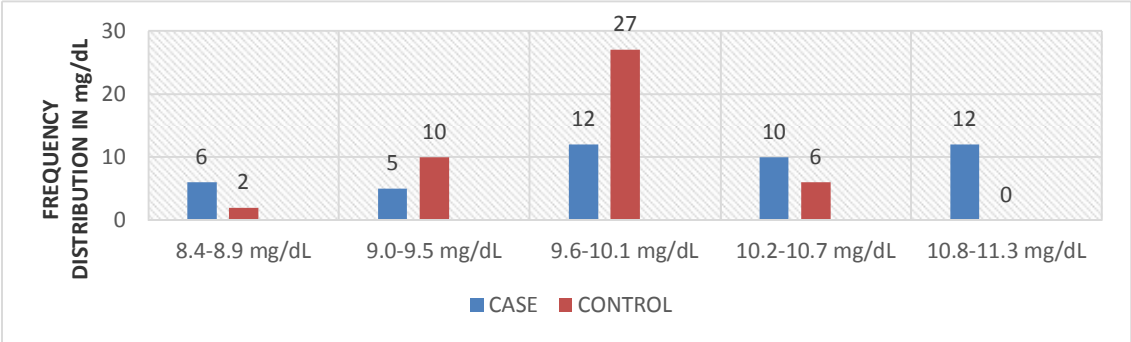

Fig. 2: Histogram for frequency distribution of serum total calcium in mg/dL

Table 5: Distribution of serum total calcium in case and control groups

Statistics	Case Group(Mg/Dl)	Control Group (Mg/Dl)	Significance
N	45	45	p =0.0085*
MEAN	10.11	9.762	t = 2.692
SEM	0.1179	0.05714	
STD. DEVIATION	± 0.7909	± 0.3833	
MEDIAN	10.1	9.8	
RANGE	8.6-11.2	8.8-10.5	

* Unpaired t-test shows p<0.05 and hence can be inferred that the difference of mean of serum calcium values of subjects in case group and control group is significant.

DISCUSSION

As estimated by WHO, depression shall become the second largest illness in terms of morbidity by another decade in the world, already one out of every five women, and twelve men have depression. Not just adults, but two percent of school children, and five percent of teenagers also suffer from depression, and these mostly go unidentified. Different pathophysiological mechanisms have been suggested via which vitamin D might be involved with the etiology or progression of depression (Ganji, *et al.,* 2010; Cherniack, *et al.,* 2009).

For instance, vitamin D might be neuroprotective (Goldstein, *et al.,* 2009) by reducing neurotoxic calcium levels in the brain (Brown, *et al.,* 2003). Because vitamin D regulates

calcium homeostasis, membrane permeability and axonal conduction, it is thought to have an indirect role in the regulation of neurotransmission.

The N-methyl D–Aspartate(NMDA) receptor is a type of ionotropic glutamate receptor, which plays an important role within the central nervous system. Normally operating NMDA receptors admit into neurons the amount of Ca^{++} ions that is vital to their function, but abnormally functioning NMDA receptors increase the cellular Ca^{++} ions beyond manageable levels leading to the activation of a series of calcium dependent enzyme systems.

The present study shows that patients of clinical depression have significantly lower values of serum 25(OH) Vitamin D as compared to control subjects (p value < 0.0001). The control group comprising of 45 healthy individuals and have a mean serum 25(OH) Vitamin D level of (32.490 ± 8.536) ng/mL and a median value of 31.400 ng/mL

The test group comprising of 45 clinically diagnosed cases of depression with a mean value of serum 25(OH) Vitamin D level of (14.001 ± 6.390) ng/mL have a median value of 12.070 ng/mL.

The results of this study reveal that the mean value of serum total calcium in test group was slightly higher than that of the control group and this difference was found to be statistically significant (p =0.0085, t =2.695). The reason for high serum calcium level in case group can also be due to an associated undiagnosed elevated parathyroid hormone (PTH) because depression is a common presentation in such cases (Mandel, 1960). Recurrent psychotic depression associated with hypocalcemia and parathyroid adenoma American Journal of Psychiatry, 117, 234-235).

CONCLUSION

From the present study, it has been found that clinically diagnosed cases of depression have lower levels of 25(OH) Vitamin D in comparison with the healthy controls. On the otherhand serum calcium is found to be increased in depression as compared to controls. Therefore, the current study implied that serum Vitamin D as well as alteration of serum calcium level play an important role in development and progression of depression & may have therapeutic implications as cautious vitamin D supplementation may decrease the severity of depression. However, more elaborate study would have been desirable to precisely establish the role of vitamin D deficiency in progression of depression.

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