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EXPLORING THE LINK BETWEEN VITAMIN D DEFICIENCY AND EPILEPSY: UNRAVELING THE CONNECTION – A COMPARATIVE STUDY

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Abstract
Objective:
1. To determine the serum levels of 25-OH vitamin D in patients of epilepsy.
2. To determine magnitude of vitamin D deficiency in the study groups and to compare the study groups with control group and among themselves.

Materials and Methods: The study was done on 136 patients, fulfilling the inclusion and exclusion criteria who were admitted to Govt Doon Medical College Hospital, Dehradun between September 2022 to October 2023 and serum levels of 25-OH vitamin D were measured of patients with epilepsy.
Results: statistically significant ($p<0.05$) values were obtained and the prevalence of vitamin D deficiency among patients with Epilepsy was 62.8% (n=27). The prevalence of insufficiency was 20.9% (n=9).
Conclusion : The association of vitamin D deficiency and Epilepsy was found to be significant and vitamin D deficiency was found to be a strong risk factor for Epilepsy.

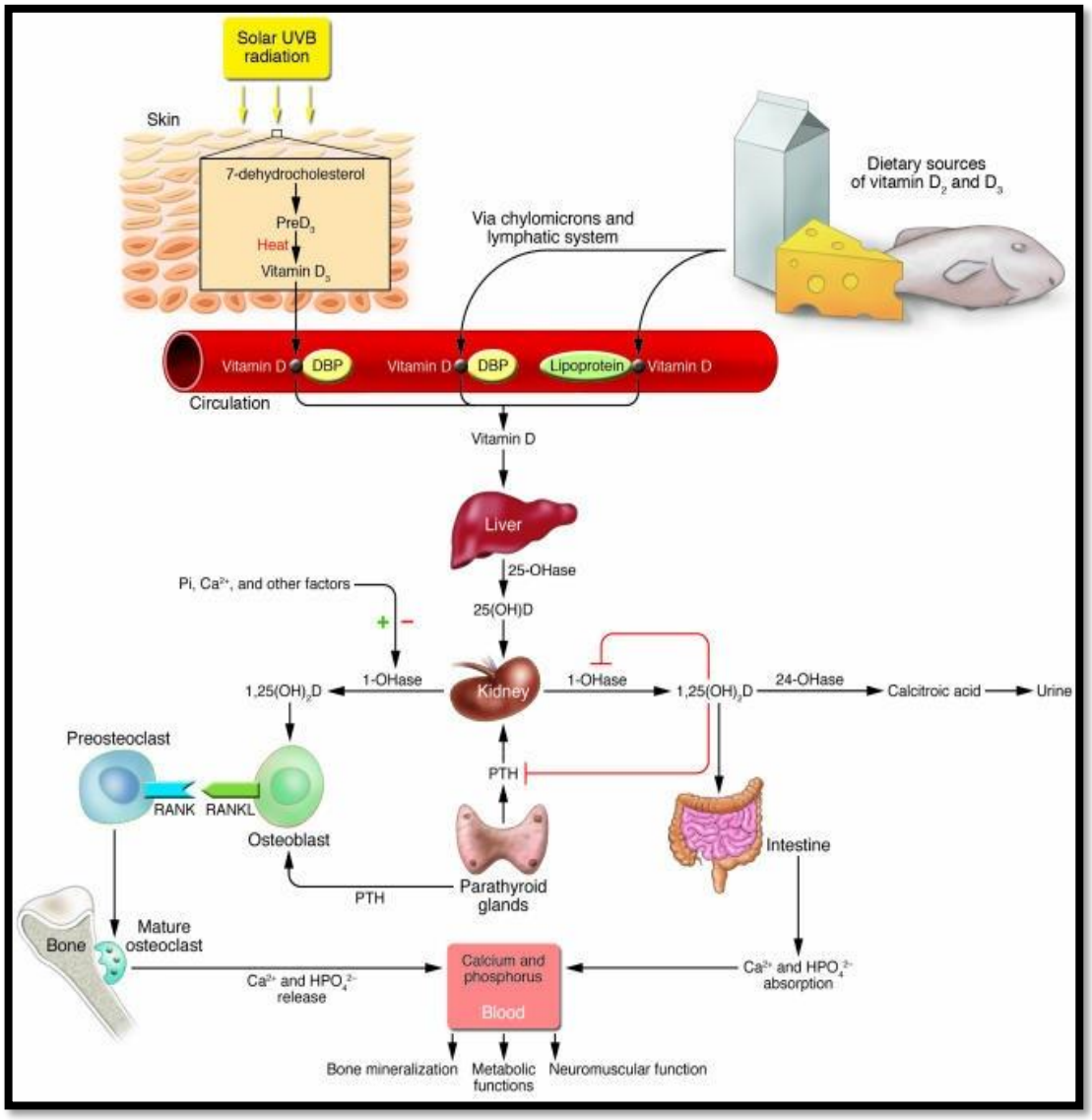
Keywords - Vitamin D, Epilepsy.

INTRODUCTION

Vitamin D, often hailed as the 'sunshine vitamin' plays a crucial role in various bodily functions, including bone health and immune system regulation. However, emerging research has shed light on a potential connection between vitamin D deficiency and epilepsy, raising intriguing questions about the impact of this essential nutrient on neurological health.
Vitamin D is a fat soluble vitamin. It is a steroid hormone that is essential for calcium and phosphate metabolism. It is naturally present in very few foods. It is produced endogenously by ultraviolet light which strikes the skin and gives vitamin D thus making it unique among all vitamins.[1] This combined with its ability to act on specific target tissues and receptors makes its classification as a steroid hormone more appropriate.
Most of vitamin D production occurs via conversion of dehydrocholesterol to previtamin D_3 by ultraviolet radiation. Previtamin D_3 is converted to cholecalciferol in skin and transported for hydroxylation firstly to 25 hydroxyvitamin D first in liver and then to 1, 25 dihydroxyvitamin D in kidney[2].

Physiology

In the human body, vitamin D is mainly found in two forms vitamin D_2 and D_3 which differ in the side chain; in contrast to D_3, vitamin D_2 has a double bond between carbons 22 and 23 and a methyl group on carbon 24. Exposure to sunlight is the major source of vitamin D for humans. The efficiency of the conversion of 7-dehydrocholesterol to vitamin D_3 depends on time of day, season of the year, latitude, skin color and age. There is little vitamin D that occurs naturally in the foodsupply that include fatty fish, beef liver and egg yolk. Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to a vitamin D binding protein. Vitamin D is not biologically active in its native form, the active from is 1,25 (OH) 2D. Vitamin D is first hydroxylated by the liver to form 25(OH)D, which is then hydroxylated by the kidney to form 1,25(OH)2D. 25(OH)D has low biological activity, but it is the major form of vitamin D that circulates in the blood stream. Serum 25(OH)D concentrations are generally thought to reflect nutritional status[2].



The photoproduction and metabolism of vitamin D and the various biologic effects.[3]

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In the presence of adequate amounts of vitamin D, the major site of 1, 25(OH)2D i.e. kidney converts some of the 25(OH)D to alternate hydroxylated metabolites having low biological activity e.g. 24,25(OH)2D or 1,24,25(OH)3D. Plasma parathyroid hormone, along with serum calcium and phosphorus concentrations regulates the renal synthesis of 1, 25(OH)2D. The enzyme 25-hydroxyvitamin D3-1-αhydroxylase, that catalyses the conversion of 25(OH)D to 1,25(OH)2D, is

also expressed by other tissues like colon, prostate, mammary glands, macrophages, antigen-presenting cells, osteoblasts and keratinocytes.

Vitamin D obtained from dietary sources and on exposure to sunlight is in the mature form. It undergoes hydroxylation in liver to 25 OH vitamin D and vitamin D_2 undergoes another hydroxylation in kidney to 1, 25 OH vitamin D.[2]

Vitamin D promotes calcium absorption in the gut so as to maintain adequate serum calcium and phosphate concentrations. This is essential for normal mineralization of bone. Vitamin D is also required by osteoblasts and osteoclasts for bone growth and remodeling[1,2]. Other important functions of vitamin D are modulation of cell growth, neuromuscular and immune function and reduction of inflammation.

Vitamin D also regulates cell proliferation differentiation and apoptosis. As per recent data reveal, 25 OH D concentrations 23nmol/lt or 12ng/ml are considered as the level for deficiency[1].

Vitamin D and Role in CNS

Several vitamin D metabolites are present in the CNS especially in substantia nigra and hypothalamus. Examples of these metabolites include 23 OH vitamin D_3, 1, 25 Di OH D3; 24, 25 Di OH D_3. It is suggested that vitamin D is a substrate for the synthesis of these substances at the above sites. Vitamin D receptors in the brain are found in cerebellum basal ganglia and hippocampus[4].Substantia nigra has the highest density of vitamin D receptors. Some other sites of vitamin D receptors in CNS include;

- Supraoptic and paraventricular nuclei of hypothalamus.
- External granule cell layer of prefrontal cortex.
- CA1 and CA2 neurons of hippocampus[4].

Function of Vitamin D in CNS

Vitamin D has a neuroprotective role in the central nerves system. Nerve growth factor which has role in growth and development of CNS is dependent on vitamin D for its biosynthesis[4,5,6]. Vitamin D may affect the development of neurons as well as their survival. It exerts its neuroprotective effect by modulating neuronal calcium and production of neurotropins[4,5].

Epilepsy and Seizures

Seizures are disturbances in brain activities characterized by abnormal firing of neurons. Vitamin D has been found to have an anticonvulsant effect which is mainly due to down regulation of cytokine IL6 considered as a procolvulsant. Vitamin D also up regulates neurotrophic factors GDNP at TN3 which also have anticonvulsant action[6].

Also there are certain calcium binding proteins which possess antiepileptic properties. Vitamin D increases the expression of those calcium binding proteins, even some trials support that vitamin D should be given prophylactically in epilepsy[6].

Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A (2012)[32]. There is growing interest concerning the role of vitamin D in various medical conditions such as diabetes and oncological, cardiovascular and central nervous system disorders. Although vitamin D deficiency is known to be highly prevalent among epilepsy patients, only a single study, published nearly forty years ago, assessed the effect of vitamin D on seizure control. Here, they measured serum 25-hydroxy-vitamin D (25(OH)D) levels and normalized it by administration of vitamin D3 in 13 patients with pharmacoresistant epilepsy. To see if vitamin D3 has an impact on seizure frequency, they compared seizure numbers during a 90-day period before and after treatment onset. They found that seizure numbers significantly decreased upon vitamin D3 supplementation. Median seizure reduction was 40%. They conclude that the normalization of serum vitamin 25(OH)D level has an anticonvulsant effect.

GC DeLuca, SM Kimball, J Kolasinski, SV Ramagopalan, GC Ebers (2013)[38] Vitamin D and its metabolites have pleomorphic roles in both nervous system health and disease. Animal models have been paramount in contributing to human knowledge and understanding of the consequences of vitamin D deficiency on brain development and its implications for adult psychiatric and neurological diseases. The conflation of in vitro, ex vivo, and animal model data provide compelling

evidence that vitamin D has a crucial role in proliferation, differentiation, neurotrophism, neuroprotection, neurotransmission.

OBJECTIVES

1. To determine the serum levels of 25-OH vitamin D in patients of epilepsy.
2. To determine magnitude of vitamin D deficiency in the study groups and to compare the study groups with control group and among themselves.

STUDY AREA

This study was conducted at Government Doon Medical College Hospital, Dehradun.

STUDY DESIGN AND PERIOD

This was a case control study. The data was collected from september 2022 to october 2023.

STUDY POPULATION

The present case control study included participants with epilepsy who reported to medical OPD or were admitted in the Postgraduate Department of Medicine, Government Medical College Dehradun.

Each participants was given written informed consent and underwent biochemical, dietary, life style and clinical assessments. Study participants completed questionnaire about life style and dietary intake including:

1. Sunlight exposure (total number of hours worked/day).
2. Use of multi vitamins, calcium and vitamin D supplements.
3. Intake of milk, curd, fish, liver, beef, butter, eggs, juices and other foods.
4. A diet description.

Sunlight exposure was estimated from questions about frequency of sunlight exposure, as well as duration of sun light exposure on working and non-working days. Serum 25(OH)-vitamin D concentrations was measured following an overnight fast using the DiaSorin LIAISON 25(OH)D

TOTAL CLIA.[3]

Operational Definitions

Vitamin D	25 OH Vitamin D (ng/ml)	25 OH vitamin D (nmol/ml)
Deficiency	< 20	< 50
Relative insufficiency	21 –29	52 –72
Sufficient	≥ 30	≥ 75

INCLUSION CRITERIA

• The prospective study included patients suffering from epilepsy.

EXCLUSION CRITERIA

1. Significant renal or hepatic dysfunction defined as a serum creatinine of > 2.5mg/dL or aspartate aminotransferase > 2.5 times normal.
2. Malabsorption including any history of inflammatory bowel disease or small bowel or gastric surgery.
3. Disease associated with altered bone metabolism (hyper-thyroidism, hyperparathyroidism and type I diabetes mellitus.
4. Known metabolic bone disease.
5. Treatment with medications that interfere with vitamin D metabolism (anti-convulsants, rifampcin and glucocorticoids, either actively taking or taken for > 2 weeks during the previous month).

METHOD OF DATA COLLECTION

After informed consent was taken from the participant, the data regarding demographic characteristics, phenotypic features, lifestyle assessment, subjective general health, dietary assessment and use of calcium or vitamin D supplements was collected using a structured questionnaire. The questionnaire was interpreted in local vernacular whenever deemed necessary. Basic anthropometric data (height, weight, BMI) was also collected.

HEALTH STATUS

Participants health status was assessed both clinically as well as based on laboratory investigations and using various imaging modalities.

LABORTORY PROCEDURE

Early morning blood sample was collected after an overnight fast Blood samples were collected via venipuncture method by trained phlebotomists who traveled to the data collection sites. There they were provided with a separate room at each location for the blood drawing process and serum 25(OH)D level was measured using DiaSorin LIAISON 25(OH)D TOTAL CLIA. The LIAISON 25(OH) Vitamin D TOTAL Assay is a direct competitive chemiluminescence immunoassay for human serum or plasma intended for use on the DiaSorin LIAISON automated analyzer. The assay uses magnetic particles (solid phase) coated with antibody against 25(OH)D and 25(OH)D conjugated to an isoluminol derivative (tracer). During the first incubation phase (10 min), 25(OH)D is dissociated from binding protein by buffer containing 10% ethanol and then binds to the anti-25(OH)D antibody on the solid phase. After a second 10 min incubation with the tracer, the unbound material is washed off and starter reagents are added to generate a flash chemiluminescent signal which is measured by a photomultiplier and is inversely related to 25(OH)D concentration. This assay differs from its older version, LIAISON 25 OH Vitamin D due to alterations in the on-board extraction procedure, the addition of a second incubation step, and the use of human serum-based calibrators instead of horse serum.

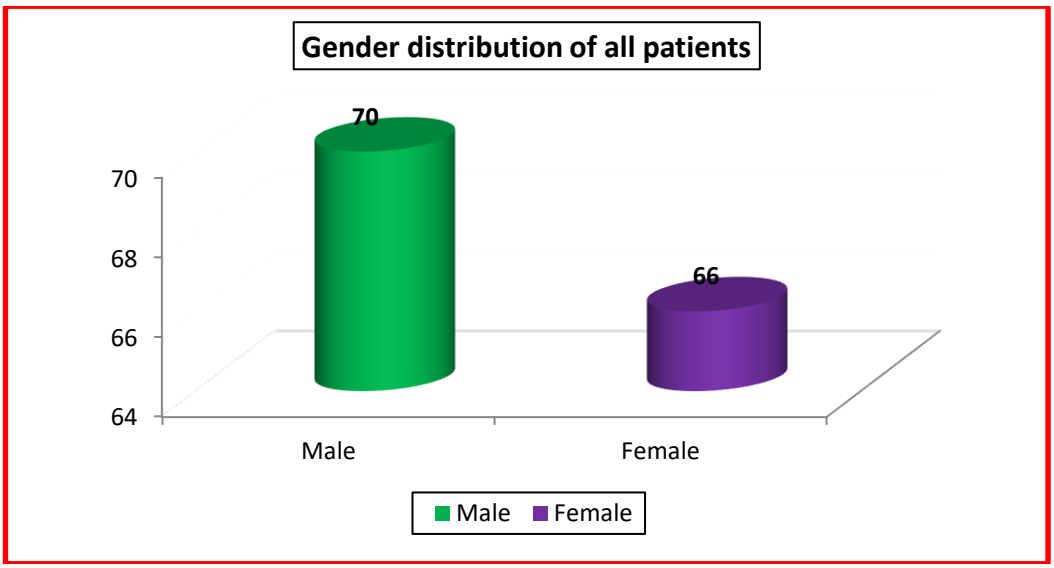
STATISTICAL ANALYSIS

Statistical package for Social Sciences (SPSS0, Version 20) and Microsoft Excel were used to carry out the statistical analysis of data. Data was analysed by means of descriptive statistics viz, percentages, means and standard deviations. Graphically the data was presented by bar and pie diagrams. Chi-square test or Fisher's exact test, whichever appropriate, was employed for comparison of qualitative data. Odds ratio was used to compare cases and controls. A P-value of less than 0.05 was considered statistically significant.

Table 1a: Mean age of all patients
Mean±SD=54.7±19.972

The mean age of all patients participating in the study was 54.7 years.

Table 1b: Gender distribution of all patients		
Gender	No.	Percentage
Male	70	51.5
Female	66	48.5
Total	136	100



The study was done on 136 patients admitted to Govt Doon Medical College Hospital, Dehradun. About 51.5 % (n=70) cases were males while 48.5% (n=66) were females.

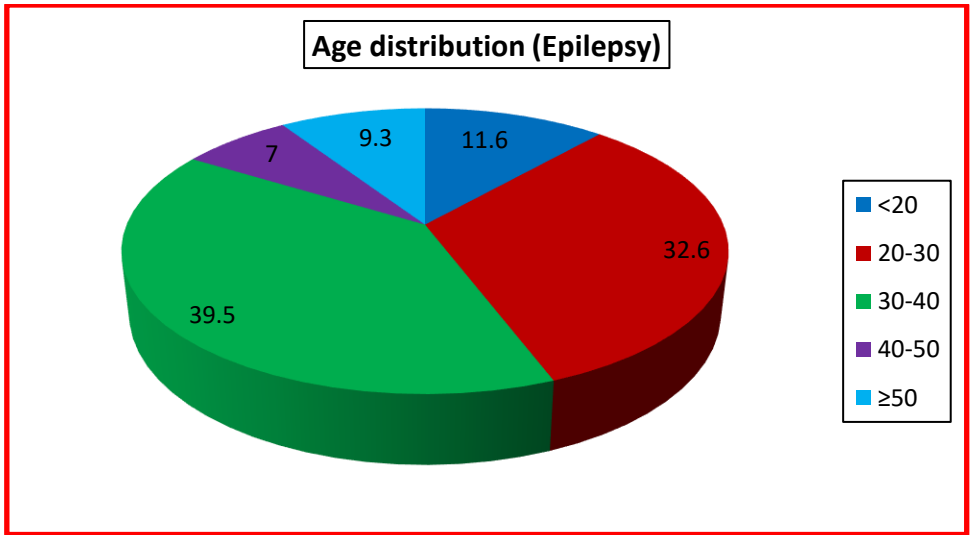
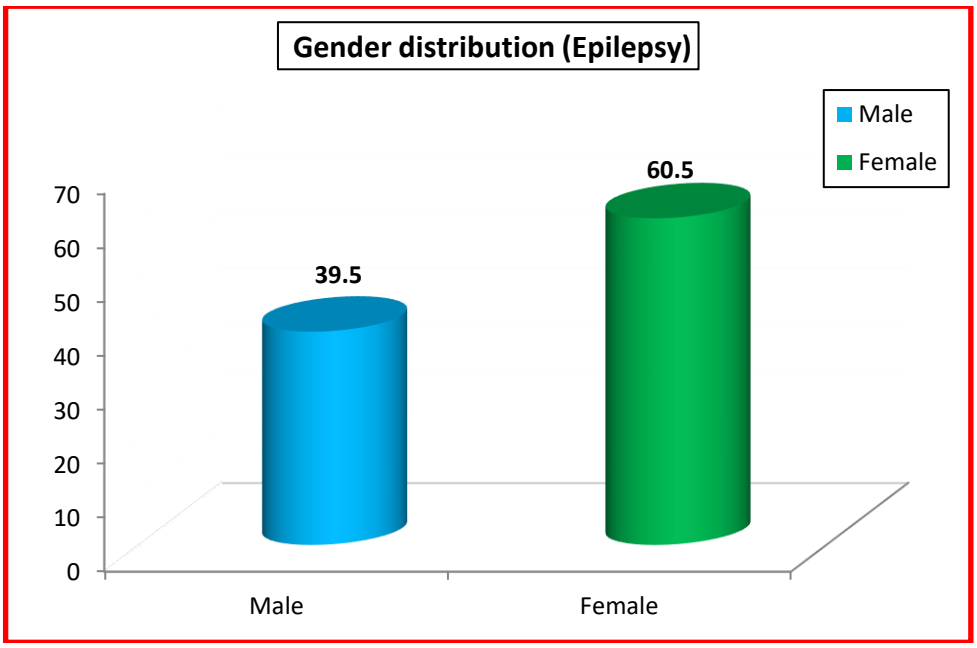


Table 7: Age distribution (Epilepsy)		
Age group	No. of patients	%age
<20	5	11.6
20-30	14	32.6
30-40	17	39.5
40-50	3	7.0
≥50	4	9.3
Mean±SD	33.16±16.713	

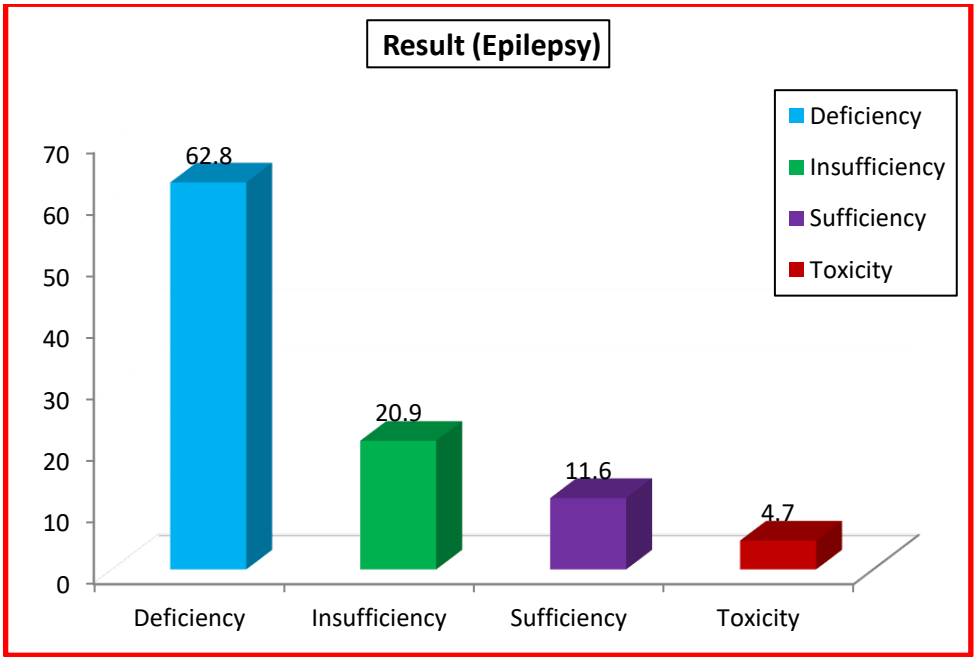
Most of the epileptic patients were falling in the 30-40 age group with mean age of 33.16 years.

Table 8: Gender distribution (Epilepsy)		
Sex	No. of Patients	%age
Male	17	39.5
Female	26	60.5
Total	43	100



Males accounted for39.5% while females accounted for 60.5% of epilepsy patients.

Table 9: Result (Epilepsy)		
Result	No. of patients	%age
Deficiency	27	62.8
Insufficiency	9	20.9
Sufficiency	5	11.6
Toxicity	2	4.7
Total	43	100



The prevalence of vitamin D deficiency among patients with Epilepsy was 62.8% (n=27). The prevalence of insufficiency was 20.9% (n=9). The prevalence of toxicity was 4.7% (n=2). 11.6% (n-5) epilepsy patients were found to have normal levels of vitamin D.

Table 10: Effect of Anticonvulsant Drugs on Vitamin D Levels					
Drug Name	**Deficiency**	**Insufficiency**	**Sufficiency**	**Toxicity**	**Total**
Phenytoin	14 (60.87%)	5	3	1	23
Carbamazepine/ Oxcarbamazepine	7 (70%)	2	1		10
Valproate	6 (60%)	2	1	1	10

Maximum vitamin D deficiency was observed in patients on carbamazepine/oxcarbamazepine (70%) followed by those on phenytoin and valproate i.e. 60.87% and 60% respectively.

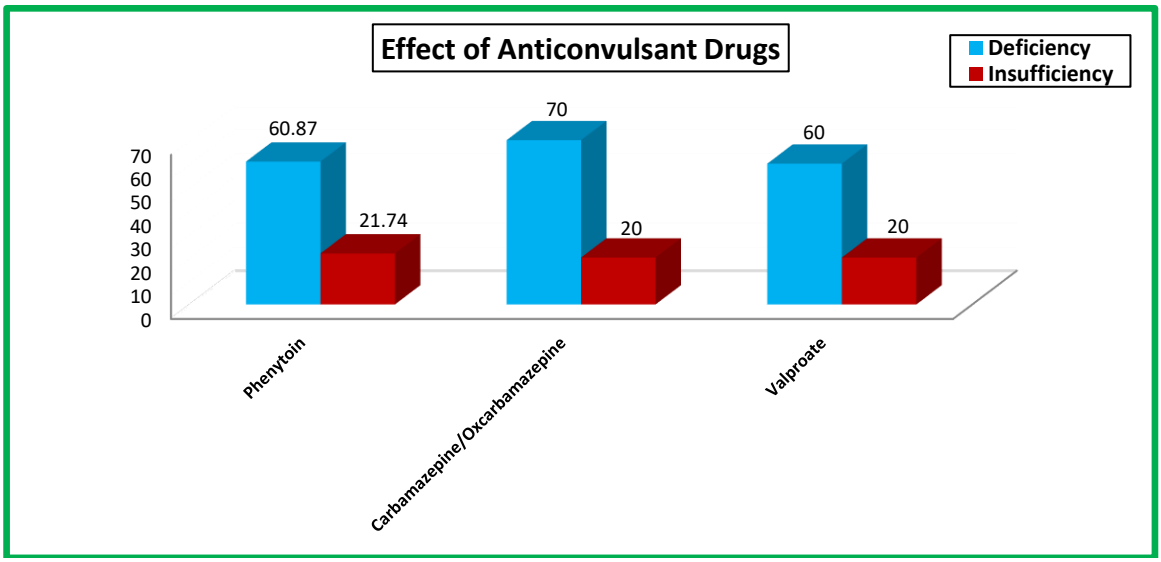
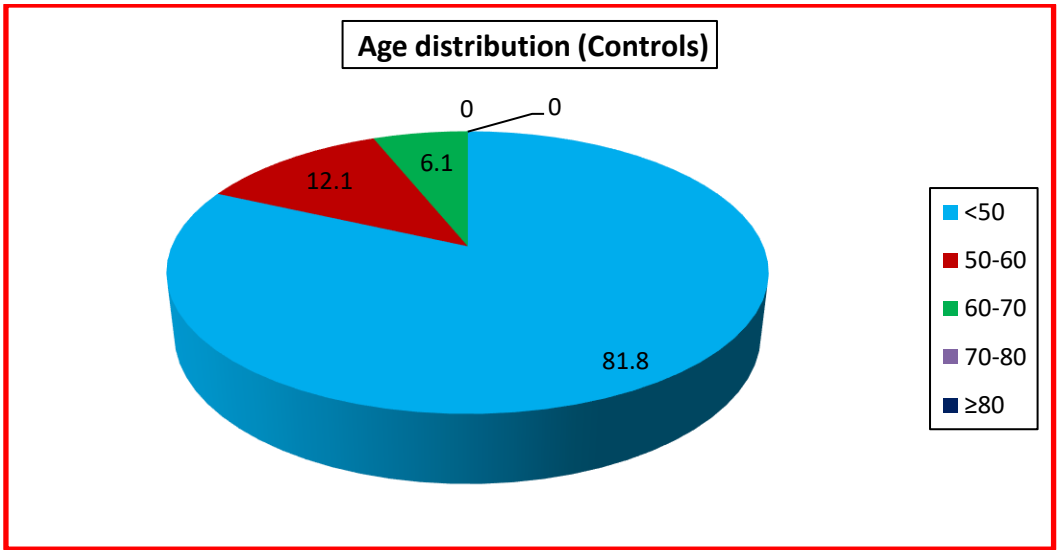
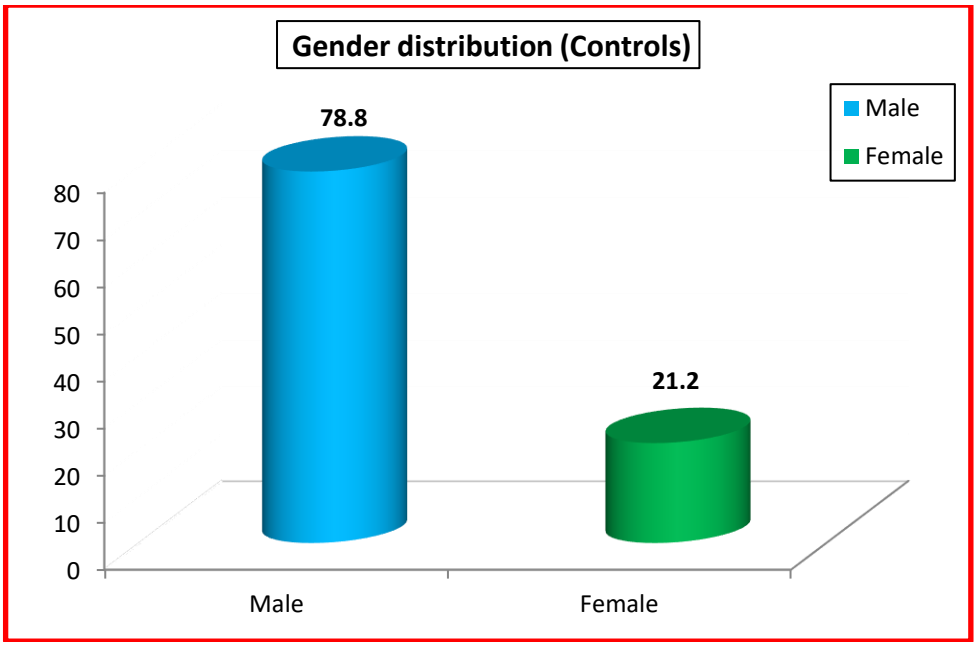


Table 24: Age distribution of controls		
Age group	No. of patients	%age
<50	27	81.8
50-60	4	12.1
60-70	2	6.1
70-80	0	0.0
≥80	0	0.0
Mean±SD	39.09±11.938	



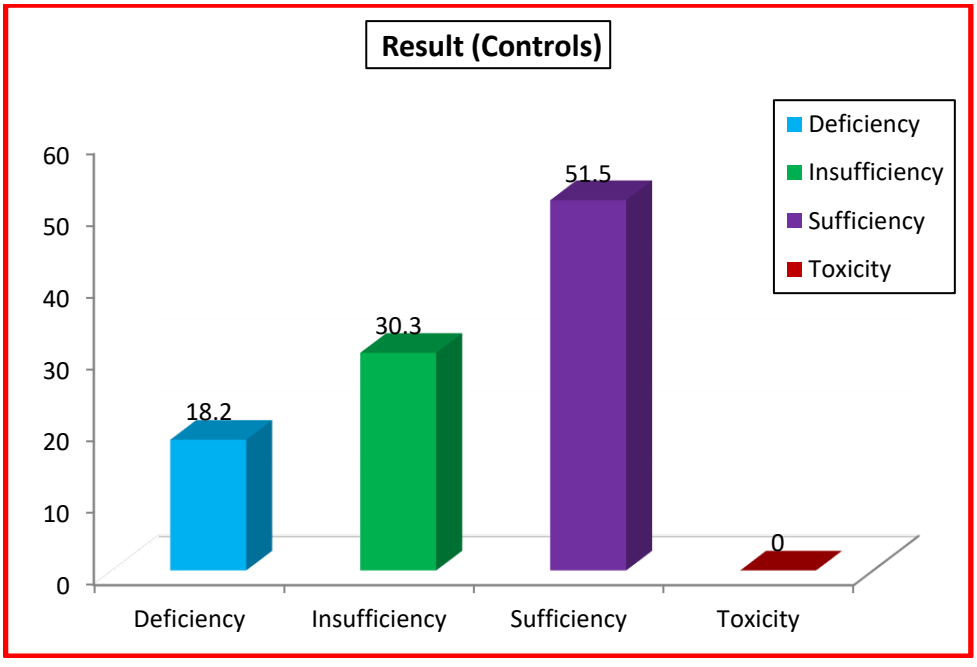
Mean age of control group was 39.081years

Table 25: Gender distribution of controls		
Sex	No. of Patients	%age
Male	26	78.8
Female	7	21.2
Total	33	100



78.8% controls were males while 21.2%were females.

Table 26: Result (Controls)		
Result	No. of patients	%age
Deficiency	6	18.2
Insufficiency	10	30.3
Sufficiency	17	51.5
Toxicity	0	0.0
Total	33	100



In the control group, vitamin D deficiency and sufficiency was detected as 18.2% and 51.5% respectively.

The prevalence of vitamin D deficiency among patients with Epilepsy was 62.8% (n=27). The prevalence of insufficiency was 20.9% (n=9). The prevalence of toxicity was 4.7% (n=2). 11.6% (n-5) epilepsy patients were found to have normal levels of vitamin D. The mean vitamin D levels were 26.9ng/ml. The prevalence of vitamin D deficiency among patients with Parkinson's disease was 46.4% (n=13). The prevalence of insufficiency was 14.3% (n=4). The prevalence of toxicity was 3.6% (n=1). 35.7% (n=10) of Parkinson's patients were found to have normal levels of vitamin D. The mean vitamin D levels were 32.3ng/ml.

EPILEPSY

In our study, the prevalence of vitamin D deficiency among patients with Epilepsy was 62.8% (n=27). The prevalence of insufficiency was 20.9% (n=9) which was significantly more than that found in controls who had deficiency of 18.2% (n=6) and insufficiency of 30.3% (n=10) respectively ($p<0.001$), thereby proving that vitamin D deficiency is associated with epilepsy. The mean vitamin D levels of patients with epilepsy was 26.9 my/ml. In the epilepsy study group the prevalence of vitamin D deficiency was more when compared to other study groups and the controls with an odds ratio of 7.59 vs the controls thereby implying that vitamin D deficiency is an independent risk factor for epilepsy.The findings in our study are supported by Hollo et al (2012)[32] who measured serum 25-hydroxy-vitamin D (25(OH)D) levels and normalized it by administration of vitamin D3 in 13 patients with pharmaco-resistant epilepsy. To see if vitamin D3 has an impact on seizure frequency, the authors compared seizure numbers during a 90-day period before and after treatment onset. They found that seizure numbers significantly decreased upon vitamin D3 supplementation. Median seizure reduction was 40%. They concluded that the normalization of serum vitamin 25(OH)D level has an anticonvulsant effect which substantiates our finding that vitamin D deficiency might be an independent risk factor for epilepsy. However in our study we didn't check the effect of vitamin D supplementation on our subjects .Moreover one cannot be oblivious to the fact that anti epileptic medications could also aggravate the vitamin D deficiency in our subjects although we had included only those patients who were either off medications or who had taken them for preceding three months. Furthermore there are studies which are in contravention with our study like the one by George Koshy et al (2013)[39]who conducted a study titled "Derangements in bone mineral parameters and bone mineral density in south Indian subjects on antiepileptic medications Vitamin D deficiency (<20 ng/mL) was found in 32 (58.1%) cases and 37 (69.8%) controls ($P = 0.234$). The difference in the above study from our study can be attributed to the fact that in the above study all the subjects including the controls had poor exposure to sunlight as reported by the authors.

STUDY STRENGTHS

The strength of the study was that this was the only study in Dehradun on the status of vitamin D in Epilepsy patients. Such studies have been done throughout the world and other parts of India. This study endorses the fact that vitamin D deficiency has a strong association with the Epileptic patients as well as is a strong risk factor for the same.

STUDY LIMITATIONS

The main limitation of the study was that this study had a small sample size. Moreover the participants were from a single institution. Also the seasonal variation in vitamin D levels was could not be assessed in our study.

The study was done on 136 patients admitted to Govt Doon Medical College Hospital, Dehradun. About 51.5 % (n=70) cases were males while 48.5% (n=66) were females.

Following **conclusions** were drawn from the study:

1. The prevalence of vitamin D deficiency among patients with Epilepsy was 62.8% (n=27). The prevalence of insufficiency was 20.9% (n=9).

2. The association of vitamin D deficiency and Epilepsy was found to be significant and vitamin D deficiency was found to be a strong risk factor for Epilepsy.

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