Estimation of Vitamin D Levels in Acute Ischaemic Stroke - A Study from Amritsar, Punjab

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ABSTRACT

BACKGROUND

World Health Organization (WHO) defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin." Low serum 25 hydroxy vitamin D is associated with large infarct volume, which worsens the outcome in ischemic stroke patients. In this study, we wanted to evaluate serum vitamin D levels in acute ischaemic stroke (AIS) patients and correlate the severity of stroke with lipid profile & central nervous system (CNS).

METHODS

It was a cross sectional comparative study, conducted in Department of Medicine in SGRDIMSR, Sri Amritsar from December 2018 to June 2020. A total of 100 subjects, 50 cases of AIS, diagnosed by history, clinical examination and supported by magnetic resonance imaging (MRI) of brain and 50 age and sex matched healthy controls were enrolled for the present study to estimate serum vitamin D level in AIS. Detailed clinical history and clinical examination were done on all participating subjects and relevant investigations were done. Diagnosis was confirmed by MRI brain in acute ischemic stroke cases. The severity of neurological impairment was evaluated as per Canadian neurological stroke scale within 24 hours of admission of the cases.

RESULTS

Mean age of cases was 62.06 ± 10.52 years and mean age of control was 59.14 ± 11.36 with maximum number of subjects were in age group of 61 - 70 years. The mean value of vitamin D in study group was 19.31 ± 9.24 while in control group, mean value was 36.42 ± 8.33, showing more serum vitamin D deficiency in cases having AIS than controls. (P value 0.021).

CONCLUSIONS

The present study suggests that the low serum vitamin D levels in the body is associated with more severe neurological deficit.

KEYWORDS

Stroke, Serum Vitamin D, Acute Ischemic Stroke, Canadian Neurological Scale

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BACKGROUND

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Vitamin D Level

Vitamin D status in relation to serum 25(OH)D levels was determined on the basis of US endocrine society classification.

Serum 25-Hydroxy Vitamin D (ng/ml)	Vitamin D Status
< 10	Severe deficiency
< 20	Deficiency
20 – 30	Insufficiency
> 30	Sufficiency

Canadian Neurological Stroke Scale

- Canadian neurological stroke scale is a simple tool to be used in monitoring of neurological status of patients with stroke in the acute phase.
- It measures deficits due to stroke.
- It measures earlier detection of deterioration.
- Scoring - 1.5 to 11.5 score
- Lower score indicative of greater neurological deficit.
- It includes the following assessments:
  1. Level of consciousness
  2. Orientation
  3. Aphasia
  4. Motor strength
- Assessments of motor functions are divided into two sections:
  1. A1 – administered if patient is able to understand and follow commands.
  2. A2 – administered in the presence of comprehension deficit.

Scores submitted from each domain section are summed to provide a total score out of a possible 11.5. Lower scores are representative of increasing severity. The data has been analysed using Statistical Package for Social Sciences (SPSS) 24.0 software. Chi square test and 't' test have been used to evaluate and interpret the data. P values less than 0.05 are considered statistically significant.

Vitamin D is an organic compound consisting of fat-soluble secosteroid mainly responsible for regulation of calcium and phosphorous levels, among other physiological functions. Calcitriol is the active form of Vitamin D that binds to the Vitamin D receptor and dimerizes with retinoid X receptor, and translocates to the nucleus to bind to Vitamin D response elements.[2]

Optimal serum concentrations of 25(OH)D for bone and general health have not been established because they are likely to vary by stage of life, by race and ethnicity, and with each physiological measure used. In addition, although 25(OH)D levels rise in response to increased vitamin D intake, the relationship is non-linear. Most people in the world meet at least some of their vitamin D needs through exposure to sunlight. Older people and people with dark skin are able to produce less vitamin D from sunlight. People can develop vitamin D deficiency when usual intakes are lower over time than recommended levels, exposure to sunlight is limited, the kidneys cannot convert 25(OH)D to its active form, or absorption of vitamin D from the digestive tract is inadequate. Diets low in vitamin D are more common in people who have milk allergy. Vitamin D plays an important role in calcium homeostasis and bone metabolism, with the capacity to modulate innate and adaptive immune function, cardiovascular function, and proliferation and differentiation of both normal and malignant keratinocytes. Ultraviolet-B (UVB) light is used to treat patients with untreated mild essential hypertension and a deficiency of vitamin D. These scientists found that UVB radiation, not UVA radiation, led to an increase in 25-hydroxyvitamin D levels and brought down blood pressure in vitamin D-deficient patients with essential hypertension.[3]

Vitamin D has neuroprotective effects against ischemic stroke. It promotes the expression of insulin-like growth factor 1, which has neuroprotective capabilities that help combat axon and dendrite degeneration, as well as antithrombotic capabilities through activation of plasminogen. Vitamin D also induces vasodilation, relieves arterial pressure, and improves post stroke blood flow to neurons by potentiation of nitric oxide synthase.[4]

Vitamin D helps regulate the renin-angiotensin-aldosterone system (and thereby blood pressure), vascular cell growth, and inflammatory and fibrotic pathways. Vitamin D deficiency is associated with vascular dysfunction, arterial stiffening, left ventricular hypertrophy, and hyperlipidemia.[5,6]

Vitamin D plays a role in glucose metabolism. It stimulates insulin secretion via the vitamin D receptor on pancreatic beta cells and reduces peripheral insulin resistance through vitamin D receptors in the muscles and liver. 1-α, 25-dihydroxyvitamin D(3) regulates the renin-angiotensin system, suppresses proliferation of vascular cell smooth muscle, improves insulin resistance and endothelial cell-dependent vasodilation, inhibits myocardial cell hypertrophy, exerts anticoagulant and antifibrotic activity, and modulates macrophage activity and cytokine generation. Overall, the high prevalence of vitamin D(3) deficiency and the plausible biological mechanisms linking this to cardiovascular disease risk suggest that the treatment of vitamin D(3) deficiency leads to prevention of cardiovascular diseases. Vitamin D might be involved in the pathophysiology of type 2 diabetes through its effects on glucose metabolism and insulin signalling as well as its ability to reduce inflammation and improve pancreatic beta-cell function.[7]

Risk factors like smoking, increased body mass index (BMI), diabetes and hypertension are significantly associated with strokes among young people. The age group for stroke in young has been variable between different studies but perhaps should be restricted to 15 - 49 years as this age group tends to have a unique set of causes and risk factors.[8]

1-α,25-dihydroxyvitamin D(3) regulates the renin-angiotensin system, suppresses proliferation of vascular cell

smooth muscle, improves insulin resistance and endothelial cell-dependent vasodilation, inhibits myocardial cell hypertrophy, exerts anticoagulant and antifibrotic activity, modulates macrophage activity and cytokine generation. Overall, the high prevalence of vitamin D(3) deficiency and the plausible biological mechanisms linking this to cardiovascular disease risk suggest that the treatment of vitamin D (3) deficiency leads to prevention of cardiovascular diseases. Vitamin D, a regulator of bone metabolism, has been linked to the pathogenesis of various clinical conditions, including diabetes.[9] Vitamin D has anti-inflammatory effects and causes attenuation of cerebral vasospasm in haemorrhagic stroke development, as measured by vessel diameter and endothelial function of the basilar artery. Anti-inflammation of myeloid and endothelial cells occurs due to Vitamin D induced activation of stromal cell-derived factor 1α, vascular endothelial growth factor, and endothelial nitric oxide synthase. Vitamin D also inhibits renin-angiotensin, a vasoconstrictor, and thus reduce blood pressure and hinders the onset of cardiovascular diseases. Vitamin D status can determine predisposition to diabetic complications including nephropathy, neuropathy and retinopathy.[10]

Aim and Objectives

1. To study serum vitamin D level in acute ischemic stroke.
2. To study serum vitamin D level in healthy individuals.
3. To compare serum vitamin D level in cases of acute ischemic stroke with those of control in order to assess the relationship of serum vitamin D level with acute ischemic stroke.

METHODS

This study was conducted in the Sri Guru Ram Das Institute of Medical Science and Research, Vallah from December 2018 to June 2020. Cases were selected from the patients admitted in the Department of Medicine of Sri Guru Ram Das Hospital, Vallah, Amritsar with diagnosis of ischemic stroke fulfilling the inclusion and exclusion criteria.

This study was a cross sectional comparative study done in total of 100 subjects. The subjects were then divided into two groups. Group A included 50 patients of acute ischemic stroke, diagnosed by history and MRI brain, group B included 50 healthy control subjects. 50 age and sex matched healthy subjects who had no prior history of cerebrovascular accidents and who met the exclusion criteria, were taken as controls.

Detailed clinical history and clinical examination were done on all participating subjects and relevant investigations were done. Diagnosis was confirmed by MRI brain in acute ischemic stroke patients. 5 ml of venous blood was collected from all 100 subjects and serum vitamin D level was estimated within 24 hours of admission for comparative study. The severity of neurological impairment was evaluated as per Canadian neurological stroke scale within 24 hours of admission of the patients. The observations and interpretations were recorded and results obtained were statistically analyzed.

Inclusion Criteria

Patients of more than 18 years of age, who were fulfilling the WHO definition of acute ischemic stroke confirmed by MRI.

Exclusion Criteria

a. Patients with haemorrhagic stroke.
b. Patients on steroids.
c. Patients already taking vitamin D supplementation.
d. Renal failure patients
e. Metabolic bone disease and patients already diagnosed with vitamin D deficiency due to unrelated causes.
f. Autoimmune disorders

Statistical Analysis

The data has been analysed using SPSS 24.0 software. Chi square test and 't' test have been used to evaluate and interpret the data. P value less than 0.05 is considered statistically significant.

RESULTS

Maximum number of cases of study group (34 %) and control (32 %) were in the age group of 61 - 70 years. Mean age of cases was 62.06 ± 10.52 years and mean age of control was 59.14 ± 11.36. Out of 50 cases of study group, 44 % were overweight and 28 % were obese and remaining 28 % of study group were of normal body weight. Out of 50 controls, 10 % were overweight and 2 % were obese and 38 % were of normal weight. Mean value of study group was 27.53 ± 3.81 and of control group was 24.48 ± 1.75. P value 0.001.

The mean value of vitamin D in study group was 19.31 ± 9.24 while in control group, mean value was 36.42 ± 8.33. Vitamin D deficiency was found in 31 (out of 50) patients in study group and only 1 (out of 50) in control group. 15 subjects (out of 50) in study group were having insufficient vitamin D level while in control group, 6 subjects (out of 50) were having insufficient vitamin D levels. 43 subjects (out of 50) in control group were having sufficient vitamin D levels while only 4 (out of 50) patients in study group were having sufficient vitamin D levels.

In study group, neurological assessment was done using Canadian neurological score, 28 (56 %) patients were having mild severity, 17 (34 %) patients were having moderate severity and 5 (10 %) patients were having severe stroke. Mean value was 7.51 ± 1.86.

In the present study, neurological assessment was done using Canadian neurological score, subjects having deficient vitamin D levels were constituted. 11 (35.48 %) subjects were having mild Canadian neurological score, 17 (54.84 %) subjects were having moderate Canadian neurological score, 3 (9.68 %) subjects were having severe Canadian

neurological score. Subjects having insufficient vitamin D levels were constituted. 4 (26.67 %) subjects were having mild Canadian neurological score, 11 (73.33 %) subjects were having moderate Canadian neurological score, and no subject was having severe Canadian neurological score. Subjects having sufficient vitamin D levels were constituted. 2 (50 %) subjects were having mild Canadian neurological score, 2 (50 %) subjects were having severe Canadian neurological score. P value 0.021 (chi square).

Age Group (Years)	Study Group		Control Group	
	No.	% Age	No.	% Age
40 - 50	11	22.00	14	28.00
51 - 60	14	28.00	13	26.00
61 - 70	17	34.00	16	32.00
71 - 80	5	10.00	6	12.00
> 80	3	6.00	1	2.00
Total	**50**	**100.00**	**50**	**100.00**
Mean	62.06 ± 10.52		59.14 ± 11.36	

Table 1. Distribution of Subjects According to Age

BMI	Study Group		Control Group	
	No.	% Age	No.	% Age
Normal (18.0 - 24.9)	14	28.00	38	76.00
Overweight (25.0 - 29.9)	22	44.00	10	20.00
Obese (≥ 30)	14	28.00	2	4.00
Total	**50**	**100.00**	**50**	**100.00**
Mean	27.52 ± 3.81		24.48 ± 1.75	
P - value (t-test)	0.001			

Table 2. Distribution of Subjects According to BMI (Body Mass Index)

Vitamin D level	Study Group		Control Group	
	No.	% Age	No.	% Age
Sufficient (> 30 ng/ml)	4	8.00	43	86.00
Insufficient (20 - 30 ng/ml)	15	30.00	6	12.00
Deficient (< 20 ng/ml)	31	62.00	1	2.00
Total	**50**	**100.00**	**50**	**100.00**
Mean ± SD	19.31 ± 9.24		36.42 ± 8.33	
P value (t-test)	0.001			

Table 3. Distribution of Subjects According to Vitamin D Levels

CNS SCORE	No. of Cases	% Age
Mild (8.0 - 11.5)	28	56.00
Moderate (5.0 - 7.5)	17	34.00
Severe (1.5 - 4.5)	5	10.00
Total	**50**	**100.00**
Mean ± SD	7.51 ± 1.86	

Table 4. Distribution of Study Group According to the Canadian Neurological Scale (CNS)

Canadian Neurological Score	Vitamin D						Mean ± SD
	Sufficient		Insufficient		Deficient		
	No.	% Age	No.	% Age	No.	% Age	
Mild (8.0 - 11.5)	2	50.00	4	26.67	11	35.48	24.37 ± 11.96
Moderate (5.0 - 7.5)	0	0.00	11	73.33	17	54.84	16.48 ± 6.27
Severe (1.5 - 4.5)	2	50.00	0	0.00	3	9.68	15.90 ± 5.14
Total	**4**	**100.00**	**15**	**100.00**	**31**	**100.00**	**19.31 ± 9.24**
P value (chi square)	0.021						

Table 5. Association of Serum Vitamin D Levels of Study Group with Canadian Neurological Scale (CNS)

DISCUSSION

In present study, Maximum number of cases of study group (34 %) and controls (32 %) were in the age group of 61 - 70 years. Mean age of cases was 62.06 ± 10.52 years and mean age of control was 59.14 ± 11.36. Study and control groups were matched on the basis of age. There was no statistically significant difference observed between ages of study and control group.

The demographic profile of our study group was quite similar to the study conducted by Jain V (2015) et al. and Gupta A et al. (2014) in which the most common age group was 55 to 64 years.[11,12]

In present study, out of 50 cases of study group, 22 cases (44 %) were overweight and 14 cases (28 %) were obese and remaining 14 cases (28 %) had normal body weight. Out of 50 controls, 10 controls (20 %) were overweight and 2 controls (4 %) were obese and 38 controls (76 %) had normal weight. Our study showed that maximum number of cases of acute ischemic stroke were obese and overweight. Mean value of BMI of study group was 27.53 ± 3.81 and of control group was 24.48 ± 1.75, P value was 0.001. Tobias Kurth et al. (2005) had observed a strong association between obesity and acute ischemic stroke.[13]

In our study group, majority of cases with acute ischemic stroke had vitamin D deficiency. In study group, 31 cases (62 %) had vitamin D deficiency and 15 cases (30 %) were in insufficient vitamin D category and 4 cases (8 %) had normal vitamin D levels and mean value of vitamin D was 19.3 ± 9.24. In healthy control group, 1 control (2 %) had vitamin D deficiency and 6 controls (12 %) were in insufficient vitamin D category and 43 controls (86 %) had normal vitamin D levels and mean value of vitamin D was 36.42 ± 8.33. This showed that most of cases of study group were vitamin D deficient/insufficient. Thus, our study had similar association as described in a study conducted by Wajda J et al. (2019) who assessed serum vitamin D levels in patients with acute ischemic stroke. 25 cases (10.4 %) had sufficient vitamin D level, 61 cases (25.4 %) had insufficient vitamin D levels, and 151 cases (62.9 %) had a severe vitamin D deficiency. The serum 25-OH-D level was significantly lower than that age and sex matched healthy subjects (9.9 ± 7.1 vs. 21.0 ± 8.7 ng/mL).[14]

In the present study group, neurological assessment was done according to Canadian neurological scale, 28 (56 %) cases had mild severity, 17 (34 %) cases had moderate severity and 5 (10 %) cases had severe stroke. Mean value of Canadian neurological score in cases of acute ischemic stroke was 7.51 ± 1.86. A study conducted by Bushnell CD et al. (2001), evaluated that patients with lower Canadian neurological scores have poor prognosis and more severe stroke. 70 Bushnell CD et al. (2001), showed that Canadian neurological scale is helpful for prospective scoring as well as retrospective assessment of initial stroke severity by doing a study on randomly selected records of patients with ischemic stroke and got significant association between severity of neurological deficit with Canadian neurological scale (P = 0.0001).[15]

In the present study group, neurological assessment was done using Canadian neurological score. As per Canadian neurological scale, group with mild Canadian neurological score included 11 cases having deficient vitamin D levels, 4 cases having insufficient vitamin D levels and 2 cases having normal vitamin D levels. Mean value of mild Canadian neurological score with vitamin D levels was 24.37 ± 11.96.

Group with moderate Canadian neurological score included 17 cases having deficient vitamin D levels and 11 cases having insufficient vitamin D levels. Mean value of moderate Canadian neurological score with vitamin D levels was 16.48 ± 6.27. Group with severe Canadian neurological score included 3 cases having deficient vitamin D, and 2 cases having normal vitamin D level. Mean value of severe Canadian neurological score with vitamin D levels was 15.90 ± 5.14. Mean value of Canadian neurological score with vitamin D levels of the whole study group was 19.31 ± 9.24 (P value 0.021). The result was found significant. We did not find any study comparing vitamin D level with Canadian neurological score in cases of acute ischemic stroke. The reason for this finding was the diverse levels of vitamin D among the subjects which showed that the parameters affect the results significantly.

CONCLUSIONS

On assessment by Canadian neurological scale, severity of neurological deficit was less when serum vitamin D level was in normal range. The present study provides evidence that low vitamin D level is associated with risk of ischemic stroke and level of vitamin D is inversely correlated with the severity of stroke. Age group of 51 - 70 years is more prone to ischemic stroke as well as vitamin D deficiency. The present study suggests that the low serum vitamin D levels in the body are associated with more severe neurological deficit. The results, thereby suggest that vitamin D screening and accordingly vitamin D supplementation should be the part of treatment protocol in acute ischemic stroke. The results, thereby suggest that vitamin D screening and accordingly vitamin D supplementation should be the part of treatment protocol in acute ischemic stroke.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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