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Vitamin D as a Predictor of Severity and Prognosis of Acute Ischemic Stroke

Akut İskemik İnmede Şiddetin ve Prognozun Öngörücüsü Olarak D Vitamini

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Abstract

Objective: The effect of vitamin D, which is a steroid hormone, on bone health has long been known. Vitamin D is also found to be associated with various diseases such as diabetes, hypertension, chronic kidney disease, coronary artery disease, and cancer. Neuroprotective effect of vitamin D makes it an important marker in clinical course of neurological diseases such as cognitive impairment, dementia and Alzheimer's disease. Vitamin D deficiency is also associated with increased risk of stroke. In this study, we aimed to show the effect of vitamin D levels on severity and prognosis of stroke.

Materials and Methods: This was a prospective, observational study conducted in a tertiary medical center in Rohtak on 200 stroke patients admitted in Medicine ward. The National Institute of Health Stroke scale (NIHSS) and modified Rankin Scale were used to assess the severity of stroke at admission and functional outcome at 3 months, respectively. The patients were divided into 4 groups on the basis of vitamin D levels.

Results: Vitamin D deficiency was associated with higher NIHSS score and independently associated with poor functional outcome. Patients with severe and mild vitamin D deficiency, and vitamin D insufficiency had 9, 6.7, and 3.9 times higher adjusted odds of poorer functional outcomes at 3 months in comparison to the patients with normal vitamin D levels ($p<0.01$) when adjusted for age, sex, alcohol, smoking, body mass index, NIHSS score, and co-morbidities.

Conclusion: Vitamin D is associated with severe stroke and poor functional outcome at 3 months. However, further studies need to be carried out to evaluate whether supplementation of vitamin D can help prevent stroke or associated morbidity and mortality.

Keywords: Vitamin D, stroke, modified Rankin Scale, NIHSS score

Öz

Amaç: Bir steroid hormonu olan D vitamininin kemik sağlığı üzerindeki etkisi uzun zamandır bilinmektedir. D vitamininin diyabet, hipertansiyon, kronik böbrek hastalığı, koroner arter hastalığı, kanser gibi çeşitli hastalıklarla da ilişkili olduğu gösterilmiştir. D vitamininin nöroprotektif etkisi, onu bilişsel bozukluk, demans ve Alzheimer hastalığı gibi nörolojik hastalıkların klinik seyrinde önemli bir belirteç haline getirir. D vitamini eksikliği ayrıca inme riskinde artışla ilişkilidir. Bu çalışmada, D vitamini düzeylerinin inme şiddeti ve prognozu üzerindeki etkisinin ölçülmesi amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif ve gözlemsel çalışma, Rohak'ta üçüncü basamak bir sağlık merkezinde serviste yatırılarak izlenen 200 inme hastası ile gerçekleştirilmiştir. *National Institute of Health Stroke scale* (NIHSS) ve modifiye Rankin ölçekleri, sırasıyla başvuruda inme şiddetini ve 3. ayda fonksiyonel sonlanımı değerlendirmek için kullanılmıştır. Hastalar D vitamini düzeylerine göre dört gruba ayrılmıştır.

Bulgular: Vitamin D eksikliği, daha yüksek NIHSS skoruyla ve bağımsız olarak kötü fonksiyonel sonlanım ile ilişkiliydi. Şiddetli D vitamini eksikliği, hafif D vitamini eksikliği ve D vitamini yetersizliği olan hastalar; yaşa, cinsiyete, alkol ve sigara kullanımına, vücut kitle indeksi değerine, NIHSS skoruna ve komorbiditelere göre düzeltildiğinde, D vitamini düzeyleri normal olan hastalara kıyasla 3. ayda sırasıyla 9, 6,7 ve 3,9 kat daha fazla kötü fonksiyonel sonlanım oranlarına sahipti ($p<0,01$).

Sonuç: D vitamini düzeyleri 3. ayda şiddetli inme ve kötü fonksiyonel sonlanım ile ilişkilidir. Bununla birlikte, D vitamini takviyesinin inmeyi veya ilişkili morbiditeyi ve mortaliteyi önlemeye katkısını değerlendirmek için ileri çalışmaların yapılması gerekmektedir.

Anahtar Kelimeler: D vitamini, inme, modifiye Rankin ölçeği, NIHSS puanı

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Introduction

Stroke is the second leading cause of death and the third leading cause of disability worldwide (1). Globally, one in four persons over 25 years of age will have a stroke in their lifetime (2). Approximately 5.5 million deaths occur due to stroke each year (3). Over 116 million years of healthy lives are lost each year due to stroke-related death and disabilities (4). Developing countries like India are currently witnessing a stroke epidemic due to poor public awareness and inadequate infrastructure for control of common modifiable risk factors such as diabetes, hypertension (HTN), low hemoglobin, atherogenic lipid profile and also due to excessive existence of non-traditional risk factors like tobacco and alcohol use. Recanalization by thrombolysis and thrombectomy is the only definitive therapy for acute stroke. Many neuroprotective agents such as hypothermia, hyperacute magnesium therapy, high dose human albumin, free radical scavengers and GABA agonists have been tried with the rationale to prevent ongoing cerebral ischemia, but these have proved to be of no or little success only (5).

The importance of vitamin D in bone health is known for long. Vitamin D has been found to be associated with diabetes, HTN, chronic kidney disease (CKD), coronary artery disease (CAD), cancer, stroke, dementia and cognitive impairment. In recent times, vitamin D has gained much attention in stroke management as the widespread distribution of 1 alpha-hydroxylase and vitamin D receptor in the human brain suggests vitamin D has effects on brain cells (6). Vitamin D deficiency is defined as a 25-hydroxy vitamin D (25-OH D) level below 50 nmol/l and vitamin D insufficiency is defined as a 25-OH D level between 50-75 nmol/l (7). Vitamin D deficiency has been demonstrated in long-term survivors and is associated with post-stroke hip fractures (8). Various studies demonstrate the low levels of vitamin D in patients presenting with acute stroke, suggesting that this deficiency has likely preceeded the stroke and may be a potential risk factor for it. A recent meta-analysis shows a 62% increased risk of stroke in individuals on the lower end of 25-OH D levels compared to those on the higher end (9).

India is a tropical country and receives ample sunshine but 50-90% of Indians are vitamin D deficient owing to their skin pigmentation, socio-cultural and dietary habits as well as genetic makeup. Several studies, mostly from developed countries, have been recently performed on the relationship between vitamin D levels and stroke risk and its severity but they have showed inconsistent results. A few studies reported low levels of vitamin D as a predictor of stroke severity, poor functional outcome and high mortality (10). In this study, we investigated whether stroke severity and functional outcomes in individuals with stroke correlated with their plasma vitamin D levels.

Materials and Methods

This was a one-year prospective, observational study conducted on 200 patients with acute ischemic stroke (AIS) admitted in the Department of Internal Medicine in Pt. B. D Sharma PGIMS, Rohtak, from January to December 2019. This study was duly approved by the Ethical committee and the post graduate board of studies of the institution. Patients aged between 18-75 years with acute infarct established on computer tomography (CT)/ magnetic resonance imaging (MRI) within 7 days of presentation were grouped as stroke cases. We excluded patients who had stroke secondary to neuro infection, malignancy, or trauma, had history of previous stroke, or had any premorbid handicap. Patients with various neurological disorders including dementia, Alzheimer's disease, multiple sclerosis, and Parkinson's disease were also excluded. Informed consent was taken from all participants. The demographic profile and risk factors of the patients were recorded. Smoking and alcohol intake habits, blood pressure and pulse rate of all patients were recorded. All patients underwent routine laboratory investigations including the serum levels of hemoglobin, urea, creatinine, calcium, albumin, fasting glucose, lipid profile, total leukocyte count, electrocardiography and chest radiograph. All patients underwent CT head scan at presentation to rule out hemorrhagic stroke. If patients had a normal CT scan, then ischemic stroke was diagnosed based on MRI. Stroke was classified into large artery atherosclerosis, cardio-embolic, small-vessel occlusion, stroke of other determined and undetermined etiology according to TOAST classification (11). The serum 25-OH D level was measured within 24 hours of admission by using ELCIA (electrochemiluminescence) method.

Patients were divided into 4 subgroups depending on absolute vitamin D levels. Patients having severe vitamin D deficiency (≤25 mmol/l), having mild deficiency of vitamin D (25-50 mmol/l), having insufficient vitamin D levels 50-75 mmol/l and having optimal vitamin D levels (>75 mmol/l) were grouped in groups A, B, C and D, respectively. Stroke severity on admission was assessed by National Institute of Health Stroke scale (NIHSS) (11). A score of 0 indicates normal function. Subjects were divided into the following five categories according to their symptoms and NIHSS score: 0= No stroke, 1-4= Minor stroke, 5-15= Moderate stroke, 16-20= Moderate to severe stroke, and 21-42= Severe stroke.

Assessment of functional outcome was performed by using 3-month modified Rankin Scale (mRS) score (12). The mRS was assessed by either face-to-face consultation or by telephone interview with the patient or their relatives. The mRS runs from 0 to 6, ranging from perfect health without symptoms to death. Subjects were further divided into 2 subgroups based on their 3-month mRS scores: Favorable outcome defined as mRS score ≤2, and poor outcome defined as mRS score ≥3 (12). Diabetes, HTN, dyslipidemia, atrial fibrillation (AF) and CAD were defined as certain covariates per standard definitions (12). Smokers were defined as those reporting daily smoking. Ex-smokers (history of smoking 1 year back) and occasional smokers were classified as non-smokers. Alcoholics were defined as those in whom the alcohol consumption was >50 g/day. Months of 25-OH D assessments were included to account for the seasonal variations in vitamin D levels.

Statistical Analysis

The results were expressed as frequency and percentages for categorical variables, and as mean ± standard deviation and median (interquartile ranges) for continuous variables. The Mann-Whitney U test, independent t-test and chi-square test were used to compare the two groups. The influence of vitamin D on poor functional outcome and severity of stroke was performed by using binary logistic regression analysis, which allows adjustment for confounding factors. Results were expressed as adjusted Odds ratio (aOR) with the corresponding 95% confidence interval (CI). For a more detailed exploration of the 25-OH D, and functional outcomes and severity of stroke, we also used multivariate analysis models to

estimate adjusted OR and 95% CIs of poor functional outcomes and severe stroke for vitamin D (severe, mild, and insufficient with normal as reference). All statistical analyses were performed with SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, U.S.A.). Statistical significance was defined as p<0.05.

Results

Baseline characteristics of study participants are summarized in Table 1. The mean age of the patients was 59.2±10.8 years. Forty-eight percent were elderly (>60 years). The male to female ratio was 2.6:1. The mean vitamin D level was 48.6±23.5 mmol/l. Fifty percentage of the patients had vitamin D deficiency. Only 24% of patients had optimal vitamin D levels. Twenty-nine patients had severe vitamin D deficiency while 71 patients had mild vitamin D deficiency. We observed that monthly variation in levels of vitamin D was not significant. Of the patients, 32.5% had large artery atherosclerosis, 21.5% small vessel occlusion, 25% cardioembolic stroke, 16.5% stroke of undetermined etiology, and only 4.5% stroke of other determined etiology. Dyslipidemia followed by HTN was the most common comorbidity. Diabetes, AF, CAD, smoking and alcohol use were other common risk factors. Of the patients, 41% had more than one comorbid disease (diabetes mellitus/HTN/AF/CKD/CAD) and 21% of the patients did not have any comorbidity. Females were older than males at the time of stroke (62.5±9.4 vs. 60.1±10.7, p=0.49) but this association was statistically non-significant. Statistically significant decrease in age was observed with increase in vitamin D levels (p<0.001).

The severity of stroke was determined based on NIHSS scale. Forty-three patients had severe stroke, 92 moderate to severe stroke, 30 mild stroke and 35 minor stroke. The median NIHSS score was 19 in patients with severe vitamin D deficiency, 15 with mild deficiency, 7.5 with insufficient vitamin D levels and 6 with optimum vitamin D levels. There was a significant difference between the groups in terms of NIHSS score (p<0.05) (Table 2). The post-hoc analysis showed that the difference was significant among all groups except group C vs. group D and group B vs. group A. Also, vitamin D levels decreased with an increase in severity of stroke, and this was significant, as shown in Table 3. Post-hoc analysis showed that the difference between vitamin D values was significant when compared between minor stroke and moderate-stroke; minor stroke and moderate to severe stroke; and minor stroke and severe stroke. Vitamin D values were not significantly different between moderate stroke and moderate-severe stroke (p=1.000), however difference in terms of vitamin D level was significant when moderate stroke was compared with severe stroke (p<0.0001). The difference in terms of vitamin D level were not significantly different when moderate to severe stroke was compared to severe stroke (p=0.040). Vitamin D deficiency was negatively correlated with NIHSS score in our study (Pearson correlation: -0.457, p<0.001).

Excellent functional outcome was observed in 53% of patients. The mRS scores showed a decreasing trend with an increase in vitamin D levels from patients with severe vitamin D deficiency to those with optimal vitamin D levels, as shown in Table 2

Table 1. Baseline characteristics of study population

	Frequency	Percentage
Age (years)		
18-30	1	0.5
31-45	18	9
46-60	85	42.5
61-75	96	48
Sex		
Male	144	72
Female	56	28
Co-morbidities		
Diabetes mellitus	60	30
Hypertension	120	60
Dyslipidemia	152	76
Hypercholesterolemia	90	45
Atrial fibrillation	45	22.5
Alcohol intake	63	31.5
Smoking	84	42
Coronary artery disease	30	15
Chronic kidney disease	40	20
Etiology of stroke		
Large artery atherosclerosis	65	32.5
Cardioembolic	50	25
Other determined causes	9	4.5
Small vessel occlusion	43	21.5
Undetermined etiology	33	16.5

Data expressed at frequency and percentages

Table 2. Comparison of NIHSS and mRS scores and severity of vitamin D deficiency

	NIHSS[#]	mRS[##]
Severe	19.0 (11.5, 23.0)	3.0 (2.0, 6.0)
Mild	15.0 (9.0, 20.0)	3.0 (2.0, 5.0)
Insufficient	7.5 (5.0, 15.5)	2.0 (0.0, 4.0)
Normal	6.0 (4.0, 14.0)	0.0 (0.0, 2.0)
p value	<0.0001	<0.0001

Data expressed as median (Q1, Q3), [#]p value<0.01 except normal vs. insufficient and mild vs. severe, [##]p value <0.05 except normal vs. insufficient and mild vs. severe. NIHSS: National Institute of Health Stroke scale, mRS: Modified Rankin Scale

Table 3. Association of mean vitamin D levels and stroke severity (National Institute of Health Stroke scale score)

Stroke severity	Vitamin D	ANOVA p value
Minor	64.0±23.0	<0.0001
Moderate	51.0±22.5	
Moderate/severe	46.4±18.1	
Severe	32.4±19.5	

Minor vs. moderate (p=0.016), minor vs. moderate to severe (p=0.007), minor vs. (p<0.0001)

Moderate vs. moderate to severe (p=1.000), moderate vs. severe (p<0.0001)

Moderate to severe vs. severe (p=0.040)

(3.0 in group A, 3.0 in group B, 2.0 in group C, 0.0 in group D, p<0.0001). We also observed that the patients with poor functional outcome had significantly lower vitamin D3 levels than the patients with excellent functional outcome (36.9±18.4 vs. 59.0±22.7; p< 0.0001). A decreasing trend in vitamin D levels was observed as functional outcome deteriorated (the vitamin D level was 62.5±19.9 in patients with mRS 0 and 35.3±20.4 in patients with mRS 6). The association of decrease in vitamin D levels with higher mRS scores was statistically significant (p<0.05). Median vitamin D levels of patients with mRS 6 was less than stroke survivors (31.5 nmol/l vs. 51 nmol/L, p=0.001) (Table 4).

Our study showed that the patients with severe vitamin D deficiency, mild vitamin D deficiency, and insufficient vitamin D level had 9, 6.7, and 3.9 times higher adjusted odds of poorer functional outcomes at 3 months in comparison to the patients with normal vitamin D levels (p<0.01) when adjusted for age, sex, alcohol intake, smoking, body mass index, NIHSS score, and co-morbidities (Table 5).

Discussion

The World Health Organisation defines stroke as the rapidly developing clinical symptoms and/or signs of local or global disturbance of cerebral functions, with symptoms lasting for more than 24 hours or leading to death with no apparent cause other than that of vascular origin (3). Stroke is often deadly, and for the majority of survivors it is disabling. While some stroke survivors recover completely and are left with no disability, others may be left with mild, moderate or severe disability. Risk of death is highest in the first week after the event, about 20-50% die within the first month and in survivors, considerable spontaneous recovery occurs up to 6 months (13). According to a Danish study of stroke survival, 836 patients with stroke were followed up and the risk of death was approximately 28% at the first month. Of the patients 60% survived 1 year and 31% survived 5 years. The study attributed excess mortality rates to other hazards such as cancer, cardiovascular disease and other diseases, suicide, or accidents (14).

Owing to the rising cost of health care and due to limited availability of organized stroke care services in South Asian countries, prevention of stroke is of utmost importance. Current therapeutic strategies for stroke management include recanalization by clot removal (thrombolysis, intra-arterial fibrinolysis, mechanical removal) and prevention of propagation of clot with aspirin and antilipemic agents. It takes some time for ischemic damage to spread from the core of the infarct. Viable ischemic tissue can be found up to 48 hours after stroke. Neuroprotective agents such as hyperacute magnesium therapy, free radical scavengers, glycine antagonists and GABA agonists intervening in one of the steps of ischemic cell injury have been tried with the rationale of preventing ongoing cerebral ischemia (4). Recently, many clinical trials are being conducted to prove the neuroprotection offered by vitamin D and its role in preventing ischemic stroke (15). Despite the mounting awareness of beneficial aspects of vitamin D, there is a pandemic of vitamin D deficiency (16). Vascular effects of vitamin D include inhibition of thrombosis and reduction in arterial calcification. Smooth muscle cells and lymphocytes express receptors for vitamin D and convert circulating 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D. 1,25-hydroxyvitamin D in turn reduces the proliferation of lymphocytes and the production of cytokines (17). This anti-inflammatory effect protects against atherosclerosis. Vitamin D decreases HTN by decreasing atherosclerosis, promoting endothelial function and suppressing the renin-angiotensin-aldosterone system (18). Vitamin D is also associated with modifying the production and release of neurotropic factors such as nerve growth factors and acetylcholine.

Vitamin D plays an important role as an antioxidant by increasing the reduced form of glutathione that protects the brain against reactive oxygen species and apoptosis caused by oxidation (19). Vitamin D also plays an important role in neuronal calcium regulation, nerve conduction and detoxification (20). The proposed biological attributes of vitamin D make its serum level a marker of severity and prognosis of ischemic stroke. Though many clinical studies indicate an association of vitamin D status with incidence of stroke, only a few studies have been conducted to evaluate the importance of vitamin D status in short-term stroke outcome. Most of these studies are conducted in Caucasians and the results are inconsistent. Thus, since India has a vast genetic and cultural diversity, we carried out this national study to assess the effect of vitamin D levels on severity and prognosis of ischemic stroke.

Since age is a strong predictor of stroke survival, we thought that potential deleterious effects of low vitamin D could be too small and insignificant to be detected in the elderly. A study by Daubail et al. (21) showed that no significant association existed between 25-OH D levels and 1-year mortality in patients aged ≥75 years. The mean age in stroke patients was 59.2±10.8 years in our study. This was consistent with other studies which showed that the mean age of stroke in low-income countries is 15 years lower

Table 4. Comparison of vitamin D levels and outcome in survivors vs. non-survivors

	Survivors	Non-survivors
Vitamin D (ng/ml)	51.0 (30.0, 72.0)	31.5 (16.9, 49.5)
p value	0.001	

Data expressed as median (Q1, Q3)

Table 5. Odds ratio for poor outcome at 3-months according to vitamin D levels at admission

Vitamin D levels[#]	Poor outcomes (94)	Unadjusted ORs (95% CI)	Adjusted ORs (95% CI)[##, ###]
Insufficient (n=52)	21	2.9 (1.1-7.3)	3.9 (1.2-12.3)
Mild (n=71)	43	6.6 (2.7-15.8)	6.7 (2.2-20.2)
Severe (n=29)	21	11.4 (3.8-33.8)	9.0 (2.3-35.6)
Normal (n=48)	9	Reference	Reference

[#]Serum levels of vitamin D in insufficient (51-75 mmol/L), mild (25-50 mmol/ml), severe (≤25 mmol/ml), and normal (>75 mmol/ml). [##]Adjusted for age, sex, alcohol, smoking, NIHSS score, and co-morbidities. [###]p value <0.01. ORs: Odds ratio, CI: Confidence interval, NIHSS: National Institute of Health Stroke scale

than in high-income countries (22). High burden of chewable tobacco, smoking, butter use, and low awareness of infections such as tuberculous meningitis may be the factors that contribute to high prevalence of stroke at a younger age.

Patients having severe vitamin D deficiency were lesser in our study as compared to other studies (23). The plausible explanation for this could be that most of the patients included in the study were farmers, having high levels of sun exposure. Also, most people in Haryana have their own dairy barns and consume high amounts of dairy products which are an important source of vitamin D. Although our patients were not severely vitamin D deficient, they still did not have optimal vitamin D levels due to their dark-colored skin and high phytate content in the diet. Hence, most of our study subjects had mild vitamin D deficiency and insufficiency.

Association of seasonal variation in vitamin D level was not significant in our study, which was consistent with other studies (24). Chaudhuri et al. (12) also conducted a study to measure the seasonal variation in vitamin D levels. Values were compared between the samples collected during summer (March to September) and during winter (October to February). They did not find any significant differences in the prevalence of 25-OH D deficiency between summer and winter samples collected from cases and controls (12).

Wang et al. (25) found a negative correlation between levels of 25-OH D and the NIHSS score (r=-0.389, p=0.000). They observed that serum 25-OH D level was an independent prognostic marker of functional outcome at discharge and survival [OR: 3.96 (2.85-7.87) and 3.36 (2.12-7.08), respectively, p=0.000 for both, adjusted for NHISS score, other predictors and vascular risk factors] in patients with AIS (25). This finding was similar to our finding that there was a negative correlation between 25-OH D levels and NIHSS scores (Pearson correlation: -0.457, p<0.001). The decreasing trend in NIHSS score was observed with an increase in vitamin D level. Serum vitamin D level in patients with excellent functional outcome was significantly higher than those with poor functional outcome at 3 months (59.02±22.7 vs. 39.96±18.43, p<0.001). The mean 25-OH D level was significantly higher in stroke survivors than those who died. Vitamin D level was inversely associated with mRS score (Pearson correlation: -0.489, p<0.000). This finding was in accordance with a Chinese study by Tu et al. (26) which suggested that 25-OH D was an independent predictor of death and poor functional outcome at 3 months in Chinese patients with AIS after adjusting for possible confounding factors. Kim et al. (27) carried out a study on 328 stroke patients to evaluate whether serum 25-OH D level was associated with poor outcome. They found that 25-OH D level was associated with poor 3-month functional outcome in patients with AIS (27). Fahmy et al. (28) conducted a case-control study on 96 subjects. They found a statistically significant difference between patient subgroups regarding initial scores of NIHSS, and the difference was significantly higher in the 25-OH D deficient group (p<0.05). After 3 months, mRS score was found to be significantly higher in the 25-OH D deficient group (p=0.000) (28). Another study showed that serum 25-OH D levels in patients with excellent functional outcome were significantly higher than in those with unfavorable functional outcome (50.2±32.7 vs. 43.9±30.0 nmol/l, p<0.05) (29). This study concluded that vitamin D deficiency was associated with increased initial stroke severity scale score and worse outcomes at 3 months (29).

Study Limitations

Our study has exclusively targeted ischemic stroke which is an advantage over most of the previously reported association studies on vitamin D and risk of stroke. Although vitamin D deficiency is a risk factor for stroke and its complications, possible use of vitamin D supplementation in the prevention and/or treatment of stroke is not proven. Interventional studies designed to address the effect of vitamin D supplementation on stroke are rare. The findings of the study by Momosaki et al. (15) suggested that oral vitamin D3 supplementation did not improve rehabilitation outcomes after acute strok. Long term interventional studies are required to see beneficial effects of vitamin D supplementation. A major limitation of our study was that it was a non-interventional study, as we did not provide stroke patients with vitamin D supplements to observe if supplementing vitamin D would have an effect on prognosis. Another limitation was that we did not exclude patients who were taking oral vitamin D tablets before the stroke.

Conclusion

In our study, vitamin D deficiency in patients with AIS was associated with increased severity of stroke. It was also independently associated with poor 3-month functional outcome. Thus, vitamin D level on admission can be considered as a potential predictor of stroke severity and short-term functional outcome at 3 months. Further studies are required to determine whether supplementation of vitamin D will help in improving post-stroke morbidity and mortality.

Ethics

Ethics Committee Approval: This study was duly approved by the Pt B D Sharma University of Health Sciences Ethics Committee (decision no:UHS/Aca-II/Eth/20/158) and the postgraduate board of studies of the institution.

Informed Consent: Informed consent was taken from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.K.A., D.J., T.P., J.S., S.D., Concept: H.K.A., D.J., Design: H.K.A., D.J., T.P., Data Collection or Processing: T.P., J.S., S.D., Analysis or Interpretation: H.K.A., D.J., T.P., Literature Search: T.P., J.S., S.D., Writing: D.J., T.P., S.D.

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References

1. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. Bull World Health Organ 2016;94:634-634A.
2. 1 in 4 People Over 25 Will Be Hit by Stroke - Drugs.com MedNews [Internet]. Drugs.com. 2020 [cited 17 August 2020]. Available from https://www.drugs.com/news/1-4-over-25-hit-stroke-79234.html
3. Lindsay MP, Norrving B, Sacco RL, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2019. Int J Stroke 2019;14:806-817.

4. Mousavi SA, Ziaei J, Saadatnia M. Magnesium sulfate in acute stroke: a randomized double-blind clinical trial. J Res Med Sci. 2004;4:158-161.
5. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat 2005;29:21-30.
6. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-1930. Erratum in: J Clin Endocrinol Metab 2011;96:3908.
7. Poole KE, Loveridge N, Barker PJ, et al. Reduced vitamin D in acute stroke. Stroke 2006;37:243-245.
8. Berghout BP, Fani L, Heshmatollah A, et al. Vitamin D status and risk of stroke: the rotterdam study. Stroke 2019;50:2293-2298.
9. Ji W, Zhou H, Wang S, Cheng L, Fang Y. Low serum levels of 25-hydroxyvitamin d are associated with stroke recurrence and poor functional outcomes in patients with ischemic stroke. J Nutr Health Aging 2017;21:892-896.
10. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
11. Julie Fussner CV. Assessing Stroke – Scores & Scales. Am Stroke Assoc 2019;1-23.
12. Chaudhuri JR, Mridula KR, Alladi S, et al. Serum 25-hydroxyvitamin d deficiency in ischemic stroke and subtypes in Indian patients. J Stroke 2014;16:44-50.
13. Truelsen T, Begg S, Mathers C. The global burden of cerebrovascular disease. Glob Burd Dis. 2000:1–67.
14. Henry Hoffman. Stroke Survival Statistics. Seabo. June 2018. Available from: https://www.saebo.com/blog/stroke-statistics/
15. Momosaki R, Abo M, Urashima M. Vitamin D supplementation and post-stroke rehabilitation: a randomized, double-blind, placebo-controlled trial. Nutrients 2019;11:1295.
16. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017;18:153-165.
17. Rigby WF, Denome S, Fanger MW. Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. J Clin Invest 1987;79:1659-1664.
18. Majumdar V, Prabhakar P, Kulkarni GB, Christopher R. Vitamin D status, hypertension and ischemic stroke: a clinical perspective. J Hum Hypertens 2015;29:669-674.
19. AlJohri R, AlOkail M, Haq SH. Neuroprotective role of vitamin D in primary neuronal cortical culture. eNeurologicalSci 2018;14:43-48.
20. Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline? Mol Aspects Med 2008;29:415-422.
21. Daubail B, Jacquin A, Guilland JC, et al. Serum 25-hydroxyvitamin D predicts severity and prognosis in stroke patients. Eur J Neurol 2013;20:57-61.
22. Bonita R, Mendis S, Truelsen T, et al. The global stroke initiative. Lancet Neurol 2004;3:391-393.
23. Wajda J, Świat M, Owczarek AJ, et al. Severity of vitamin d deficiency predicts mortality in ischemic stroke patients. Dis Markers 2019;2019:3652894.
24. Brøndum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 25-hydroxyvitamin D and symptomatic ischemic stroke: an original study and meta-analysis. Ann Neurol 2013;73:38-47.
25. Wang Y, Ji H, Tong Y, Zhang ZB. Prognostic value of serum 25-hydroxyvitamin D in patients with stroke. Neurochem Res 2014;39:1332-1337.
26. Tu WJ, Zhao SJ, Xu DJ, Chen H. Serum 25-hydroxyvitamin D predicts the short-term outcomes of Chinese patients with acute ischaemic stroke. Clin Sci (Lond) 2014;126:339-346.
27. Kim C, Lee SH, Lim JS, et al. Impact of 25-hydroxyvitamin D on the prognosis of acute ischemic stroke: machine learning approach. Front Neurol 2020;11:37.
28. Fahmy E, Sharaf S, Helmy H, Sherif S. Vitamin D status in acute ischemic stroke: relation to initial severity and short-term outcome. Egypt J Neurol Psychiatry Neurosurg. 2019;55:1-6.
29. Park KY, Chung PW, Kim YB, et al. Serum vitamin D Status as a predictor of prognosis in patients with acute ischemic stroke. Cerebrovasc Dis 2015;40:73-80.