

Relation of Vitamin D Deficiency to Ischemic Stroke in Compare to Normal Population

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Abstract: *Background:* 25-hydroxyvitamin D deficiency is a novel CV risk factor, predicting both CV events and mortality. This study aimed to investigate the relationship between serum vitamin D levels in ischemic stroke patients in compare to normal population. *Method:* 217 patients with ischemic stroke (CT scan confirmed) were selected for analysis between ages 45 and 80 yrs., admitted at our hospital. Measurements of serum vitamin D concentration were made by electrochemiluminescence immunoassay and Confounding variables like diabetes, hypertension, smoking, alcohol, tobacco, dyslipidemia, BMI, CRP, S. uric acid, duration of sunlight exposure, prior history of drug intake or fracture, S. calcium, phosphorous and PTH levels were considered. 200 age and sex matched controls were taken. The sources of data were questionnaires and multiple linear regression analysis and correlation analysis were used. *Result:* Vitamin D deficiency was higher in cases (87%) as compared to controls (78%) and this association was found to be statistically significant (Chi square = 5.409, df=1, P < 0.01 and Odds Ratio=0.5253 (95% CI: 0.3125 to 0.8828)). *Conclusion:* Serum vitamin D level is significantly reduced in patients of ischemic stroke as compare to control. Vitamin D is a potential risk factor for stroke and vitamin D supplementation could be used for better outcome in ischemic stroke patients with vitamin D deficiency.

Keywords: Vitamin D, Ischemic Stroke

1. Introduction

Stroke is the second leading cause of death among people aged 60 years and above.^[1] and is causing a substantial global disease burden. Based on the global burden disease (GBD) 2013 study, about 6.5 million people died from stroke and 10.3 million people suffered a stroke in 2013.^[2] Increasing risk of symptomatic ischemic stroke with decreasing plasma 25-hydroxyvitamin D concentrations has been seen.^[3] Serum 25-hydroxyvitamin D [25(OH) D] levels are inversely associated with important cardiovascular disease (CVD) risk factors.^[4] However the association between 25(OH)D levels and prevalent CVD has not been extensively examined in the general population. Serum 25(OH) D level is an independent predictor of functional outcome in patients with acute ischemic stroke.^[5] Altered calcium homeostasis, including vitamin D deficiency, was found to be associated with subclinical atherosclerosis and low bone mineral density.^[6] Low vitamin D levels have been associated with increase in intima media thickness.^[6] Vitamin D insufficiency has been linked to cardiovascular diseases, infections, and even cancer in recent large epidemiological studies.^[7] Low serum levels of 25-hydroxyvitamin D (25(OH) D) is also shown to be associated with insulin resistance.^[8] Studies have also demonstrated that 25-hydroxyvitamin D deficiency is a novel CV risk factor, predicting both CV events and mortality.^[9] Vitamin D deficiency is associated with changes in PTH, calcium, phosphorus, and 1, 25-dihydroxyvitamin D levels (1, 25[OH]D).^[10] The mechanisms by which vitamin D deficiency affects cardiovascular health are being investigated.^[11] Carotid atherosclerosis leading to increased carotid artery intima media thickness is an important factor in ischemic stroke patients.^[12] The associations between VDD and higher hsCRP levels and between 25(OH) D levels and poor outcome at short-term in acute ischemic stroke patients suggest the important role of vitamin D in the inflammatory response and pathophysiology of this ischemic event in some studies.^[13]

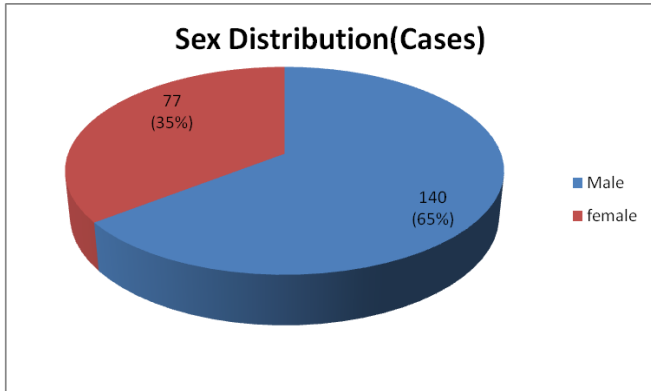
2. Material and Method

This was a case control study where all confirmed cases of ischemic stroke admitted from Neurology clinic, OPD and Medicine wards of our hospital included in this study. Age and sex matched controls not having ischemic stroke were taken after informed consent. Age group >30 years irrespective of sex with diagnosis of ischemic stroke by CT scan or MRI brain were included in the study and patients with valvular heart disease, cardiomyopathy, congenital heart disease and connective tissue disorders were excluded. Detailed history and clinical examination focusing on carotid bruit, BMI & BP were taken. Serum vitamin D (25-hydroxy vitamin D) level was measured by chemiluminescence method by Architect i1000SR Machine (Abbott laboratories, Abbott park, IL 60064 USA) from morning fasting sample. Serum 25-hydroxy vitamin D <20ng/ml was considered as deficient and >30ng/ml as adequate.^[20] Serum uric acid, serum calcium, phosphorus, PTH level, cardiac markers, CRP, complete blood count, serum creatinine, BUN, Liver function tests, serum electrolytes, blood sugar (Fasting, Post prandial) and lipid profile were measured by automated analyzers. HIV by ELISA was done. CT scan of Head (plain), Doppler ultrasound of carotid arteries (using MEDISON Sonoace X8 ultrasound machine) (Medison Co Ltd, 1003 Daechi-dong, Gangnam-gu, SEOUL 135-280 Korea) was done. EEG (wherever feasible and indicated) and MRI Brain (wherever feasible and indicated), Carotid Doppler ultrasound were done. A multiple frequency (5 to 12MHz) linear array transducer attached to a MEDISON Sonoace X8 ultrasound machine was used to acquire images by a single-sonographer blinded to clinical status of the subjects. The intima media thickness was measured in a plaque free region 20mm from the bifurcation and an average of three measurements from each side was recorded according to Mannheim Carotid Intima-Media Thickness Consensus (2004–2006).^[14] The source of data were questionnaires and multiple linear regression analysis and correlation analysis were used.

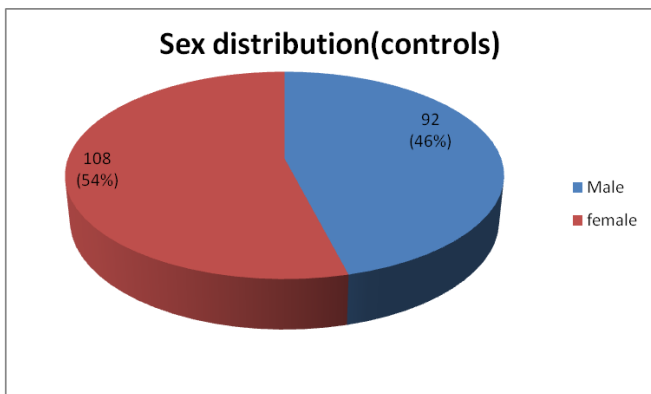
3. Result

Total number of patients included in this study were 417, out of these 217 case of ischemic stroke and 200 control were taken. Total duration of study was 2 years.

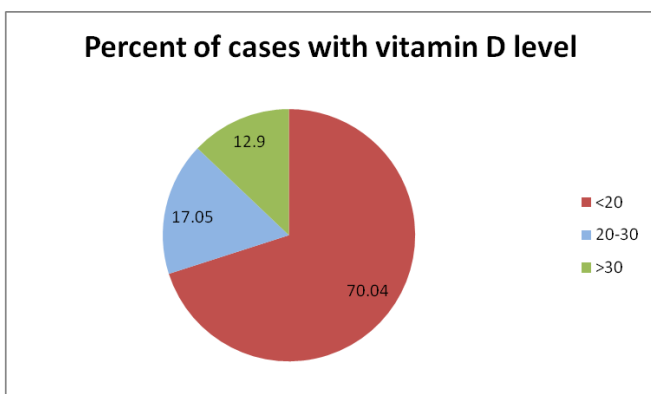
Among the cases 65% (140) were male and 35% (77) were female. (Figure 1)



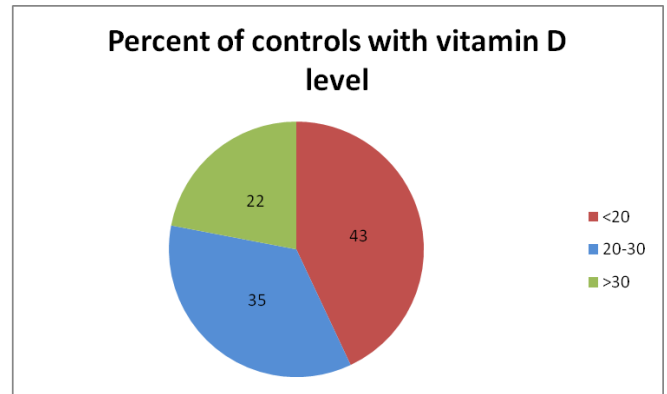
Among the control 46 % (92) were male and 54 % (108) were female. (Figure 2)



Among the cases 70.04% had vitamin D deficient, 17.05% had insufficient vitamin D and 12.9% had normal vitamin D level. (Figure 3)



Among the control 43% had vitamin D deficiency, 35% had vitamin D insufficiency and 22% had normal vitamin D. (Figure 4)



Mean vitamin D level in cases was 19.142+/- 9.453 SD ng/ml whereas in controls it was 23.974 +/- 13.125 SD ng/ml. This association was found to be statistically significant (t = 4.338 DF=415 P=<0.0001) (table 1)

Table 1: Vitamin D levels in cases and controls

Parameter	Vitamin D(ng/ml) in cases	Vitamin D(ng/ml) in controls
Mean	19.142	23.974
N	217	200
Standard deviation	9.453	13.125

12.9% cases had adequate vitamin D levels whereas 87.1% cases had vitamin D deficiency. 22% controls had adequate vitamin D levels whereas 78% controls had vitamin D deficiency. Vitamin D deficiency was higher in cases(87%) as compared to controls(78%) and this association was found to be statistically significant(Chi square = 5.409, df=1, P < 0.001 and Odds Ratio=0.5253(95% CI:0.3125 to 0.8828)) (table 2)

Table 2: Comparison of deficiency of vitamin D in cases and controls

Vitamin D(ng/ml)	Cases	Controls	Total
<20	189(87.1%)	156(78%)	345
>30	28(12.9%)	44(22%)	72
Total	217	200	417

Mean intima media thickness in cases was 0.7894 +/- 0.09 SD mm whereas in controls it was 0.4937 +/- 0.07 SD mm .This association was found to be statistically significant (t= 34.899 df= 415 P <0.0001) (table 3)

Table 3: Average IMT in cases and controls

Parameter	Average IMT(mm) in cases	Average IMT(mm) in controls
Mean	0.7894	0.4937
N	217	200
Standard deviation	0.09861	0.07088

There is a significant negative association between average IMT and vitamin D levels in cases but the correlation coefficient is -0.3624(r= -0.3624, P<0.0001), although in patients of vitamin D deficiency Carotid intima medial thickness is increased but this was statistically not correlated

4. Discussion

Our study was a case control based study where we found significant negative association between vitamin D levels in

patients of ischemic stroke in compare to control. We also considered other confounding variables like diabetes, hypertension, smoking, alcohol, tobacco, dyslipidemia, BMI, CRP, S. uric acid, duration of sunlight exposure, prior history of drug intake or fracture, S. calcium, phosphorous and PTH levels. In our study majority of the subjects were deficient in vitamin D similar to that stated by Lips Pet al,^[16] where serum 25(OH) D was lower with higher latitudes and with darker skin types. India and China had more prevalence of vitamin D deficiency (serum 25(OH) D<25 nmol/l) as compared to Japan and South-East Asia. Supplementing vitamin D in milk can be considered in deficient areas. Verdoia M et al included patients undergoing elective coronary angiography,^[17] whereas we included all patients with ischemic stroke and non-stroke individuals. The data from our study suggested that there was an inverse correlation of vitamin d level in ischemic stroke patients in compare to control. Some study also suggested that low Vitamin D Linked to More Severe Stroke and poor outcomes.^[18] A study conducted by Zhou, Ren et al revealed that lower vitamin D status was associated with an increased risk of ischemic stroke.^[19] In another meta-analysis demonstrated a linear, inverse association between circulating 25(OH)-vitamin D ranging from 20 to 60 nmol/L and risk of CVD.^[20] Recently, a Mendelian randomized study was conducted to explore the causal relationship between serum vitamin D and the risk of ischemic stroke.^[21] Although the study did not support that serum vitamin D was a causal factor for ischemic stroke, the authors did declare that only odds ratios of more than 1.5 could be found with 80% power. Many studies have provided evidence for possible mechanisms to explain the effect of vitamin D on stroke. Although vitamin D is known for its regulation of bone health, vitamin D receptor (VDR) was expressed in most human tissues and cells.^[22] More importantly, VDR also exists in the vascular smooth muscle cell,^[23] the platelet,^[24] and many other immune cells.^[25] Since these cells play important roles in the development of stroke, they may be a possible mechanism that links vitamin D and stroke. Experiments on animals also observed that vitamin D could inhibit thrombosis.^[26] which could be supporting evidence to explain why vitamin D status increases low the risk of ischemic stroke. In addition, low vitamin D status has been associated with the up-regulation of the renin-angiotensin system (RAS), both in experimental mice^[27] and in healthy humans.^[28] RAS is a vital pathway in the regulation of the cardiovascular system. Thus, the regulation of the RAS may be another possible mechanism through which vitamin D affects the risk of stroke. Inflammation, which could drive the progress of cardiovascular diseases,^[29,30] could also be regulated by vitamin D. Vitamin D could inhibit the production of inflammation factors, such as interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-),^[31] and as a result affect the progress of stroke. Vitamin D is a potential risk factor for stroke and vitamin D supplementation has better outcome in ischemic stroke patients with vitamin D deficiency. Single dose replacement of vitamin D has significantly improved the outcome of ischemic stroke. Screening for vitamin D status is essential in ischemic stroke patients and supplementation to be done to maintain vitamin D at normal level.^[32] In our study low vitamin D level was observed in 87 % of cases in compare to 78% of

controls. In our study Intima media thickness was also increased and directly correlated in vitamin D deficient cases in compare to control, hence it could be another factor for occurrence of ischemic stroke in vitamin D deficient patients. Whereas further studies are required to confirm this association and to explore the association among different subtypes.

5. Conclusion

Serum vitamin D level is significantly reduced in patients of ischemic stroke as compare to control. Vitamin D is a potential risk factor for stroke and vitamin D supplementation could be used for better outcome in ischemic stroke patients with vitamin D deficiency.

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