

Association of Low Vitamin D Levels with Acute Ischemic Stroke

Azhar Saeed¹, Mazhar Ali Naqvi², Muhammad Azhar Shah⁴ and Saadia Shahzad³

ABSTRACT

Objective: To determine association between low vitamin-D levels and acute ischemic stroke in patients presenting in tertiary care hospital.

Study Design: Case control study.

Place and Duration of Study: This case conducted at the Services Hospital, Lahore, Multan Medical and Dental College Multan and Akhtar Saeed Medical and Dental College, Lahore from 28-05-13 to 28-12-13.

Materials and Methods: This study included 200 subjects and divided into 2 groups (cases and controls). Blood sample for Vitamin-D levels were collected and sent to institutional laboratory and results were followed to determine association of low vitamin-D levels with acute ischemic stroke.

Results: Low vitamin-D levels were found in 85% patients of stroke, and in 70% of normal subjects ($p=0.009$; odds ratio 2.42). Mean vitamin D levels for cases were 35.33 (minimum 12 and maximum 110) and 43.55 (minimum 11, maximum 132) for control group.

Conclusion: Frequency of low vitamin-D levels is higher in stroke patients compared to normal subjects in our population. So, it is recommended to treat vitamin-D deficiency adequately in order to reduce the risk of stroke.

Key Words: Stroke, Vitamin-D deficiency, Acute ischemic stroke

Citation of article: Saeed A, Naqvi MA, Shah MA, Shahzad S. Association of Low Vitamin D Levels with Acute Ischemic Stroke. *Med Forum* 2017;28(2):99-102.

INTRODUCTION

Stroke is one of the most common causes of death worldwide and results in a large proportion of physical disability.¹ Data shows that 20% of stroke survivors require institutional care after 3 months and 15%-30% are permanently disabled.² Prevalence of stroke is high in Asians.³

Several independent risk factors of ischemic stroke have been recognized. The most common of these include hypertension, diabetes mellitus, smoking, atrial fibrillation, coronary artery disease and dyslipidemias.⁴ With growing evidence, vitamin-D deficiency has been studied extensively and now considered an independent risk factor for cardiovascular disease and stroke.

Vitamin-D deficiency is common, especially in Asian countries. Several studies have demonstrated the high prevalence of low vitamin-D levels in Asians. This high prevalence has been associated with lack of proper diet, poor calcium intake, social customs and traditional clothing.

Thus, South Asian population is especially more prone to vitamin-D deficiency and its consequences.

Vitamin-D deficiency causes rickets, birth defects, osteoporosis, osteoarthritis, osteomalacia, chronic pain and muscle pain. Recent trials have considered vitamin D deficiency as a risk factor in diseases, such as cardiovascular diseases, stroke, hypertension, neurological disorders, autoimmune diseases, depression and cancer.⁵

Vitamin-D deficiency is one of the independent risk factors for acute ischemic stroke. Stroke is a leading cause of disability in adults and every year millions of stroke survivors have to adapt to a more restricted and dependent life style. This poses high socio-economic burden, especially in developing countries. Identification and thus early management of risk factors of stroke can help ameliorate this burden of disease.

Different trials have studied association of low vitamin-D levels with acute ischemic stroke. The association is population dependent, since prevalence of vitamin-D deficiency is different in different populations. Regarding the association of low vitamin-D levels with acute ischemic stroke, no data is available from our population. This study is intended to make an estimate of this association in Pakistani population which will help establish and modify guidelines for prevention of ischemic strokes.

MATERIALS AND METHODS

This case control multi-centre study was conducted at Services Hospital Lahore, Multan Medical and Dental College Multan and Akhtar Saeed Medical and Dental

¹ Department of Medicine, Medical and Dental College Multan.

² Department of Pulmonology / Medicine³, Services Institute of Medical Sciences, Lahore.

³ Department of Medicine, Akhtar Saeed Medical and Dental College, Lahore

Correspondence: Mazhar Ali Naqvi, Senior Registrar of Pulmonology, Services Institute of Medical Sciences, Lahore.
Contact No: 0332-4766873
Email: naqvisedmazharali@yahoo.co.uk

College Lahore, in six month duration from 28-05-13 to 28-12-13. This study included 200 subjects and divided into 2 groups (cases and controls). Blood sample for Vitamin D levels were collected and sent to institutional laboratory and results were followed to determine association of low vitamin-D levels with acute ischemic stroke. All ethical issues were addressed and informed consent was taken. All this information was recorded in a pre-designed proforma.

Data was collected and compiled in the computer and analyzed using SPSS-20. A quantitative variable like age was expressed as mean \pm standard deviation. Qualitative variables like gender and low vitamin-D levels were expressed as proportions and percentages. Odds ratio was calculated to determine the significant difference in both groups. Odds ratio of more than 1 was considered significant.

RESULTS

There were 64 males and 36 females in patients with stroke. In the control group, there were 59 males and 41 females. P value was calculated to be 0.281. There mean age of the subjects were 54.86 ± 13.361 years (Table 1). Table-2 compares percentages of low vitamin-D levels in both groups and statistically significant results were obtained. Low vitamin-D levels were found in 85% patients with stroke, while 70% control subjects had low vitamin-D levels. P value was .009 and odds ratio calculated to be 2.42.

Table No.1: Descriptive statistics of subjects

Variable	Case		Control	
	No.	%	No.	%
Gender				
Male	64	64.0	59	59.0
Female	36	36.0	41	41.0
Age (years)				
20-40	10	10.0	14	14.0
41-60	70	70.0	58	58.0
61-80	20	20.0	28	28.0

Table No.2: Low Vitamin-D in both Groups

Group	Male	Female	total
Case	85	15	100
Control	70	30	100
Total	155	45	200

P value: 0.009

Odds Ratio: 2.42

DISCUSSION

Studies on causes of death from the 1990s have demonstrated that stroke remains a leading cause of death. In 2001, it was predicted that stroke accounted for 5.5 million deaths worldwide, corresponding to 9.6% of all deaths.⁶ In these mortalities, two-third deaths occurred in people living in developing countries and 40% were aged less than 70 years.

An epidemiological review on stroke prevalence in nine Asian countries reported that the percentage of ischemic and hemorrhagic strokes varied from 17% to 33%.⁷ The causes of stroke are multifactorial. One of the significant proposed risk factor is vitamin-D deficiency. Vitamin-D deficiency is extremely common in our population and the prevalence is on the rise. A causal relationship between stroke and vitamin-D deficiency has been known and investigated for some time now.

Multiple gene-regulatory functions in the body are served by Vitamin-D. Almost 3,000 genes are recognized that are upregulated by vitamin-D. Different mechanisms are postulated that play role in ischemic stroke. Vitamin-D reduces the risk of arterial stiffness which is a major risk factor for stroke. Other functions of vitamin-D include increase in natural anti-inflammatory cytokines, suppression of vascular calcification and inhibition of vascular smooth muscle growth. This study included 200 patients. 100 patients with acute ischemic stroke and 100 normal subjects were recruited. The study population had comparable age distribution in both groups, with mean age of 54.86 ± 13.361 years (Table 1). The incidence of stroke increases with increasing age, and these results were in accordance with these evidences.^{8,9}

Out of 200 subjects, there were 123 males and 77 females, 64% males and 36% females were present in Case Group (patients with ischemic stroke). In the Control Group (normal individuals) 59% males and 41% females were present (Table 1). There was no significant difference in gender distribution among these two groups (p value 0.281). These results supported the epidemiological evidence that stroke incidence is approximately 25% higher in men than in women.¹⁰

Serum vitamin-D levels of less than 50 nmol/l were considered significant in our study, as considered generally by investigators.¹¹⁻¹⁴ 85% stroke patients and 70% normal subjects had vitamin-D deficiency in this study. Low vitamin-D levels are prevalent particularly in Asians as demonstrated by different studies. Around 69%-82% of the South Asian populations in India have low levels of vitamin-D.¹⁵⁻¹⁷

Data from North India revealed that vitamin-D deficiency was found in 96% of neonates¹⁸, 91% of healthy school girls¹⁹, 78% of healthy hospital staff¹⁶ and 84% of pregnant women (168) with similar results from Pakistan.^{20,21} In Bangladeshi women prevalence was 38% in high income and 50% in low income group.²²

This deficiency is present not only in South Asians living in India and Pakistan^{15,16,17,20}, but also in immigrants of South Asian origin in UK, Denmark and Norway.²³⁻²⁸ Thus apart from poverty, other causes are also taken into account, e.g. use of unbalanced diet, excessive cooking and limited exposure to the sunshine.

Some of the secondary causes pointed out by Powell and Greenberg included decreased skin synthesis due to dark pigmentation or excessive clothing, gastrointestinal problems leading to malabsorption²⁹, impaired hepatic 25 hydroxylation of vitamin D-3 (due to anticonvulsant drugs, theophylline, isoniazid or severe liver disease), impaired renal hydroxylation of 25-hydroxy vitamin D-3 due to chronic renal failure or hypoparathyroidism.²⁹ Major causes of vitamin-D deficiency³⁰, that might be specific to South Asian populations, must be studied further.

Comparison between two groups in this study (Table 2) revealed that a high proportion of stroke patients had insufficient vitamin-D compared to healthy controls (85% vs 70%, $p=0.009$). These results were statistically significant and proved that vitamin-D deficiency is independently associated with acute ischemic stroke (odds ratio 2.42; 95% CI; $P=0.009$). This association was compared with the results of pre-existing studies.

In a study conducted in Singapore, researchers compared serum vitamin-D levels between Asian ischemic stroke patients. Results showed that 95% stroke patients and 84% healthy controls had insufficient vitamin-D levels ($p=0.007$). According to a study conducted in Addenbrooke's Hospital, vitamin-D levels of 44 patients with acute ischemic stroke were compared with those of 96 healthy subjects. 77% of stroke patients were found deficient in vitamin D.³¹

A recent large population-based prospective study tested the hypothesis that low vitamin-D is associated with an increased risk of ischemic stroke in the general population. It was observed that there is a stepwise increasing risk of ischemic stroke with decreasing vitamin-D levels.³² Data from another prospective study in women provided evidence that low vitamin-D levels are modestly associated with risk of stroke.³³ Balden et al indicated that vitamin-D deficiency exacerbates stroke severity, that involves both dysregulation of the inflammatory response as well as suppression of IGF-I.³⁴

Literature from Pilz et al favors that vitamin-D supplementation is a promising approach for the prevention and treatment of strokes³⁵. Evidence from another study validated that higher vitamin-D intake was associated with lower stroke incidence. Low serum levels of vitamin-D and decreased intake were significantly predictive of stroke when adjusted for age, gender, smoking and functional capacity.³⁶

Literature provides enough data on prevalence of vitamin-D deficiency and its association with ischemic stroke. However, no such data on this association was available in our population. This study is an effort to provide primary data for further research work. Local guidelines should be made regarding routine screening and early treatment of vitamin-D deficiency.

CONCLUSION

Frequency of low vitamin-D levels is higher in stroke patients compared to normal subjects in our population. So, it is recommended to treat vitamin-D deficiency adequately in order to reduce the risk of stroke.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Samiullah S, Humaira M, Hanif G, Ghouri AA, Shaikh K. Etiological patterns of stroke in young patients at a tertiary care hospital. *J Pak Med Assoc* 2010;60(3):201-4.
2. Goldstein L, Adams R, Alberts M, Appel L, Brass L, Bushnell C, et al. Primary prevention of ischemic stroke. *Stroke* 2006; 37(6): 1583--1633.
3. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, et al. A prospective community-based study of stroke in Kolkata, India. *Stroke* 2007;38(3):906-10.
4. Antonios N, Angelillo DJ, Silliman S. Hypertriglyceridemia and ischemic stroke. *Eur Neurol* 2008;60(6):269-78.
5. Masood SI, Iqbal MP. Prevalence of vitamin-D deficiency in South Asia. *Angiogenesis* 2008;1(11):12.
6. World Health Organization. The World Health Report: 2002: Reducing risks, promoting healthy life. WHO, 2002.
7. Stroke epidemiological data of nine Asian countries. Asian Acute Stroke Advisory Panel (AASAP). *J Med Assoc Thai* 2000;83(1):1-7.
8. Scarborough P, Peto V, Bhatnagar P, Kaur A, Leal J, Gray A et al. Stroke statistics 2009. Oxford, UK: British Heart Foundation; 2011.
9. DeSilva DA; Talabucon LP, Ebonne Y Ng, Tan EK, Wong TY, et al. Vitamin-D levels are lower in acute ischemic stroke patients compared to matched controls. *Stroke* 2013; 44:AWMP5
10. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, et al. Coronary heart disease statistics 2012 edition. BHF 2012:P107.
11. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporosis Int* 2005;16(7): 713-6.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3):266-81.
13. Thomas MK, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT. Hypovitaminosis-D in medical inpatients. *N Engl J Med* 1998;338(12):777-83.
14. Lips P. Vitamin-D deficiency and secondary hyperparathyroidism in the elderly. *Endocr Rev* 2001;22(4):477-501.

15. Harinarayan C. Prevalence of vitamin-D insufficiency in postmenopausal south Indian women. *Osteoporosis Int* 2005;16(4):397-402.
16. Arya V, Bhambri R, Godbole MM, Mithal A. Vitamin-D status and its relationship with bone mineral density in healthy Asian Ind *Osteoporosis Int* 2004;15(1):56-61.
17. Harinarayan C, Ramalakshmi T, Venkataprasad U. High prevalence of low dietary calcium and low vitamin-D status in healthy south Indians. *Asia Pac J Clin Nutr* 2004;13(4):359-64.
18. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin-D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr* 2005; 81(5):1060-4.
19. Puri S, Marwaha RK, Agarwal N, Tandon N, Agarwal R, Grewal K, et al. Vitamin-D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi. *Br J Nutr* 2008; 99(4):876-82.
20. Atiq M, Suria A, Nizami S, Ahmed I. Vitamin-D status of breastfed Pakistani infants. *Acta Pædiatr* 1998;87(7):737-40.
21. Rashid A, Mohammed T, Stephens W, Warrington S, Berry J, Mawer E. Vitamin-D state of Asians living in Pakistan. *Br Med J* 1983;286(6360):182.
22. Islam M, Lamberg-Allardt C, Kärkkäinen M, Outila T, Salamatullah Q, Shamim A. Vitamin-D deficiency. *Eur J Clin Nutr* 2002;56(1):51-6.
23. Roy DK, Berry JL, Pye SR, Adams JE, Swarbrick CM, King Y, et al. Vitamin-D status and bone mass in UK South Asian women. *Bone* 2007;40(1): 200-4.
24. Andersen R, Mølgaard C, Skovgaard T, Brot C, Cashman K, Jakobsen J, et al. Pakistani immigrant children and adults in Denmark have severely low vitamin-D status. *Eur J Clin Nutr* 2007;62(5): 625-34.
25. Shaunak S, Colston K, Ang L, Patel SP, Maxwell J. Vitamin-D deficiency in adult British Hindu Asians: a family disorder. *Br Med J* 1985; 291(6503):1166.
26. Holvik K, Meyer H, Haug E, Brunvand L. Prevalence and predictors of vitamin-D deficiency in five immigrant groups living in Oslo, Norwa.. *Eur J Clin Nutr* 2004;59(1):57-63.
27. Falch J, Steihaug S. Vitamin-D deficiency in Pakistani premenopausal women living in Norway is not associated with evidence of reduced skeletal strength. *Scand J Clin Lab Invest* 2000;60(2): 103-9.
28. Meyer HE, Falch JA, Sjøgaard AJ, Haug E. Vitamin D deficiency and secondary hyperparathyroidism and the association with bone mineral density in persons with Pakistani and Norwegian background living in Oslo, Norway. *Bone* 2004;35(2):412-7.
29. Powell HS, Greenberg D. Tackling vitamin-D deficiency. *Postgrad Med* 2006;119(1):25.
30. Joint F. Vitamin and mineral requirements in human nutrition. 2005.
31. Poole KE, Loveridge M, Barker PJ, Halsall DJ, Rose C, Reeve J, et al. Reduced vitamin-D in acute stroke. *Stroke* 2006;37(1):243-5.
32. Brøndum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 25-Hydroxyvitamin-D and symptomatic ischemic stroke. *Ann Neurol* 2013; 73(1):38-47.
33. Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-Hydroxyvitamin-D levels and the risk of stroke: prospective study and meta-analysis. *Stroke* 2012;43(6):1470-7.
34. Balden R, Selvamani A, Sohrabji F. Vitamin-D deficiency exacerbates experimental stroke injury and dysregulates ischemia-induced inflammation in adult rats. *Endocrinol* 2012;153(5):2420-35.
35. Pilz S, Tomaschitz A, Drechsler C, Zittermann A, M Dekker J, Marz W. Vitamin-D supplementation: a promising approach for the prevention and treatment of strokes. *Curr Drug Targets* 2011; 12(1):88-96.
36. Marniemi J, Alanen E, Impivaara O, Seppänen R, Hakala P, Rajala T, et al. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr Metab Cardiovasc Dis* 2005;15(3):188-97.