Original Article

The Association Between Vitamin D Deficiency and Stroke

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Objective: To determine the association between vitamin D deficiency and stroke in patients admitted in Mayo Hospital, Lahore.

Methods: Two hundred (200) subjects taken as one hundred (100) stroke patients (cases) and one hundred (100) controls comprised the sample using Non-probability, Consecutive Sampling Technique. Serum 25 (OH) Vitamin D levels were checked in all the subjects.

Results: Out of a total of 200 subjects, 2(2%) in both the groups were between the age group of 18-40 years, 37(37%) of the cases and 41(41%) of the controls fell in the 41-50 years age group while 61(61%) of the cases and 57(57%) of the controls were between 51-60 years of age. Mean±SD for the age distribution was calculated to be 50.87±6.19 for cases and 50.90±6.07 for controls. Gender distribution of the subjects was recorded as 39(39%) for male cases and 45(45%) for male controls while 61(61%) were female cases and 55(55%) were female controls. Frequency of type of stroke was recorded as ischemic stroke in 72(72%) cases while 28(28%) of the cases were suffering from hemorrhagic stroke. No stroke in control subjects was reported. Comparison of vitamin D deficiency in both groups revealed 61(61%) in cases and 29(29%) in controls while 39(39%) in cases and 71(71%) in controls had no vitamin D deficiency. Odds ratio was calculated as 3.8294, p value was 0.0001 which showed a significant difference between the two groups. Stratification for vitamin D deficiency according to age showed that out of 61 subjects in cases group, 27(44.26%) were under 50 years of age and 34(55.74%) were over 50 years of age and p value was 0.20 which was statistically insignificant. In 29 control subjects, 12(41.38%) were under 50 years and 17(58.62%) were over 50 years of age, p value was 0.18. Stratification for vitamin D deficiency according to type of stroke was done and it showed that out of 61 subjects in cases group, 43(70.49%) had ischemic stroke and 18(29.51%) had hemorrhagic stroke, p value was 0.0001, showing statistically significant difference. All the 29 control subjects were healthy without any type of stroke.

Conclusions: Vitamin D deficiency is significantly higher in stroke patients as compared to healthy controls. It is a potential risk marker for stroke, and the role of vitamin D repletion in enhancing musculoskeletal health after stroke needs to be explored and emphasized.

Keywords: association, vitamin D deficiency & stroke

Introduction

Vitamin D is the major steroid hormone that regulates mineral ion hemostasis. Two forms of vitamin D exist namely ergocalciferol (D2) and cholecalciferol (D3). D2 is derived from plant sources whereas D3 is obtained from animal sources. The liver produces 25-(OH) vitamin D or calcidiol which is the intermediate precursor to the metabolically active 1,25(OH) vitamin D, also called calcitriol.[1,2]

Vitamin D, in addition to maintaining calcium hemostasis and bone health, also has several important functions e.g., insulin secretion, immune modulation, cell proliferation and cell differentiation via inhibition of matrix metalloproteinases.[3,4] Vitamin D also optimizes neuromuscular and skeletal function, has an impact on intestinal absorption of calcium and phosphorus, renal excretion of phosphate, and bone resorption.[5]

Common dietary sources of vitamin D include milk and dairy products. Oily fish is one of the richest dietary sources of vitamin D. Several foods are fortified with vitamin D, including many cereal products, which contain 50 IU of vitamin D per serving. Most multivitamins include 400 IU of vitamin D per tablet.

Vitamin D deficiency has become significantly prevalent worldwide. It tends to occur in almost every age group but is more common among children and adolescents. Normal Vitamin D levels are in the range of 30-100ng/ml. Levels <20ng/ml are considered deficient whereas levels between 21-29ng/ml are

Labelled as insufficient.

Vitamin D deficiency has implications in the pathophysiology of many chronic diseases. Apart from rickets, cancer, stroke, cardiovascular disease, obesity and autoimmune conditions like multiple sclerosis, asthma, type 1 diabetes, all have been linked with vitamin D deficiency.[6]

Vitamin D insufficiency is significantly high in the elderly, institutionalized and hospitalized individuals but several studies have found a high prevalence of vitamin D deficiency among healthy, young adults as well. Also vitamin D levels show varied degree of fluctuation throughout the year, with the highest levels occurring after the summer and the lowest concentrations after winter. These seasonal variations may also affect males, people living at high latitudes and those who do greater physical activity. The major factors predisposing to vitamin D deficiency are inadequate dietary intake and sun exposure. Other factors that may contribute to vitamin D deficiency include severe malnutrition, liver failure, nephrotic syndrome, gastrointestinal diseases that lead to malabsorption, acquired immunodeficiency syndrome with hypocalcemia. Patients who have mild vitamin D deficiency may have only muscle weakness or pain or decreased bone density apart from modest decreases in serum calcium or phosphate levels, or both. Levels of alkaline phosphatase and parathyroid hormone (PTH) may be elevated in these patients but in some patients, PTH levels may be entirely normal.

Stroke is the leading cause of disability worldwide and is the second most common cause of death after ischemic heart disease.[7,8] The incidence of stroke is decreasing in the developed countries owing to the advancement in healthcare, but in the developing countries, the incidence is still increasing. More than 5.5 million deaths are attributed to stroke annually with two thirds of these occurring in the developing world. There are no sizeable community based epidemiological studies in Pakistan to substantiate this assertion, but stroke is considered to be the first leading cause of disability and the third most common cause of death in the developing countries.[9]

Stroke is defined as an "acute neurologic deficit of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain".[10] There are two main types of stroke, ischemic accounting for 85% and hemorrhagic, accounting for approximately 15% of all cases of stroke.[11]

Multiple etiologies contribute to the development of ischemic stroke and may have variable clinical manifestations. Out of the different causative factors, small or large artery thrombus account for approximately 45% whereas 20% of ischemic strokes are embolic in origin. The remainder have an unknown cause.[11] Long bone surgeries and cardiac surgery may dislodge emboli in the form of blood, fat, or air resulting in embolic strokes.[12]

Risk factors for stroke include smoking, hypertension, heart disease, diabetes, dyslipidemias. Less common causes of ischemic stroke include carotid artery dissection or the presence of coagulopathies e.g., the one resulting from antiphospholipid antibodies. Other causes include infections, periodontal disease and tooth loss, arteritis, and drug abuse, such as the use of amphetamines and cocaine.[11]

Strokes may occur at any age but are much more common in the older population. The death rate doubles every ten years between the ages of 55 to 85 years. Because of this fact as well the distribution of the population according to their age, about 3/4th of all stroke related deaths occur in individuals over the age of 65 years.[13] Over the last decade, a 100% increase has been observed in the risk of stroke in low and middle income countries and 85.5% of mortality due to all stroke related deaths occur in the developing world. The prevalence of stroke in Pakistan is reported to be 4.8%.[14,15]

Methods

This Case-Control Study was conducted by the Departments of Medicine and Neurology of Mayo Hospital, Lahore from 12th June, 2013 to 11th December, 2013. A sample size of 200 subjects (100 cases and 100 controls) was calculated with 80% power of test and 5% level of significance keeping the expected percentages of vitamin D deficiency as 52.94% in cases and 39% in the control group. Non-Probability Consecutive Sampling technique was applied. Subjects (both cases and controls) of either sex, between the age group of 18-60 years were included in the study. Cases were labelled as all patients presenting with stroke having confirmatory evidence through CT/MRI (Brain) whereas Controls were all the healthy attendants of the patients admitted either with stroke or any other condition, falling in the same age group and gender as that of the cases. Cases excluded from the study were patients with the history of Vitamin D malabsorption

Patients with celiac sprue, short bowel syndrome, cholestatic liver disease, cystic fibrosis etc. Also patients with history of taking medication, associated with vitamin D deficiency, such as Phenytoin, Phenobarbital, and Rifampin which could induce hepatic P450 enzymes to accelerate the catabolism of vitamin D as well as patients having stroke due to space occupying lesions confirmed through CT/MRI Brain, infections or bleeding diathesis having confirmatory evidence through specific blood tests were also excluded from the study. The controls who were excluded from the study were all the persons on calcium and vitamin D supplementation, persons with a history of ischemic heart disease, hypertension, diabetes mellitus, hypercholesterolemia, stroke, chronic kidney disease and chronic liver disease.

One hundred (100) patients admitted with stroke in the Medical & Neurology Departments of Mayo Hospital and one hundred (100) healthy controls conforming to the inclusion criteria were included in the study. All the subjects were informed about the purpose of the study and the willingness of the subjects was considered as consent for enrollment in the study. The risks and benefits were explained to the subjects prior to their enrollment. After obtaining informed consent from the subjects, detailed history was taken followed by clinical examination, necessary laboratory investigations and CT/MRI (Brain), serum sample was drawn for measurement of 25-(OH) vitamin D levels. The sample was analyzed using Siemens Advia Centaur Immunoassay System IRL 46350440 by the Advanced Diagnostic Centre, King Edward Medical University, Lahore. All the collected information was entered in a predesigned proforma. For the purpose of ethical consideration and exercising secrecy requirements, the subject identifiers were removed after the initial completion of proforma, prior to data analysis to take care of confidentiality and anonymity. No monetary benefit was provided to the studied subjects, only the dissemination of medical knowledge that could benefit society as a whole was reckoned to be the possible indirect benefit to the patients.

The collected data was analyzed using SPSS version 17.0. The variables included age and sex of the patient and vitamin D levels. Mean and Standard deviation was calculated for quantitative variables like age etc. Frequency and percentages were calculated for qualitative variables like sex and vitamin D levels. Odds ratio (OR) was calculated to measure the strength of association between vitamin D deficiency and stroke. Odds ratio greater than 1 was considered statistically significant. Effect modifiers like age (<50 years, >50 years) and type of stroke (hemorrhagic, ischemic) were addressed through stratification.

Results

Out of a total of 200 subjects, 2(2%) in both the groups were between the age group of 18-40 years, 37(37%) of the cases and 41(41%) of the controls fell in the 41-50 years age group while 61(61%) of the cases and 57(57%) of the controls were between 51-60 years of age. Mean+SD for the age distribution was calculated to be 50.87±6.19 for cases and 50.90±6.07 for controls. Gender distribution of the subjects was recorded as 39(39%) for male cases and 45(45%) for male controls while 61(61%) were female cases and 55(55%) were female controls. Frequency of type of stroke was recorded as Ischemic stroke in 72(72%) cases while 28(28%) of the cases were suffering from hemorrhagic stroke. No stroke in control subjects was reported. Comparison of vitamin D deficiency in both groups revealed 61(61%) cases and 29(29%) in

Table-1: Comparison of vitamin d deficiency in cases and controls based on age, gender and the type of stroke

Age Distribution (Years)	Cases (n=100)	Controls (n=100)
18-40	2 (2%)	2 (2%)
41-50	37 (37%)	41 (41%)
51-60	61 (61%)	57 (57%)
Mean± SD	50.87± 6.19	50.90± 6.07
Gender Distribution		
Males	61 (61%)	55 (55%)
Females	39 (39%)	45 (45%)
Type of stoke		
Ischemic	72 (72%)	0 (0%)
Hemorrhagic	28(28%)	0 (0%)
No stoke	0 (0%)	100 (100%)
Vitamin D Deficiency		
Yes	61(61%)	29 (29%)
No	39(39%)	71 (71%)
ODDS Ratio:3.8294	P-value: 0.0001	

Table-2: Stratification of vitamin d deficiency according to age and type of stroke.

Age Distribution (Years)	Cases (n=61)	Controls (n=29)
>50	27 (44.26%)	12 (41.38%)
>50	34 (55.74%)	17 (58.62)
Total	61 (100%)	29 100%)
	p-value: 0.2	
Type of stoke		
Ischemic	43 (70.49%)	0 (0%)
Hemorrhagic	18 (29.51%)	0 (0%)
Total	61 (100%)	0 (0%)
	p-value:0.0001	

Controls while 39(39%) in cases and 71(71%) in controls had no vitamin D deficiency. Odds ratio was calculated as 3.8294, p value was 0.0001 which showed a significant difference between the two groups. Stratification for vitamin D deficiency according to age showed that out of 61 subjects in cases group, 27(44.26%) were under 50 years of age and 34(55.74%) were over 50 years of age and p value was 0.20 which was statistically insignificant. In 29 control subjects, 12(41.38%) were under 50 years and 17(58.62%) were over 50 years of age, p value was 0.18. Stratification for vitamin D deficiency according to type of stroke was done and it showed that out of 61 subjects in cases group, 43(70.49%) had ischemic stroke and 18(29.51%) had hemorrhagic stroke, p value was 0.0001, showing statistically significant difference. All the 29 control subjects were healthy without any type of stroke.

Discussion

The role of vitamin D in calcium metabolism is of pivotal significance[16] and many serious diseases may be attributed to vitamin D deficiency e.g., cardiovascular disease and cancer.[17] The risk of fractures and bone loss may further be augmented by reduced vitamin D levels. Significant associations between low levels of vitamin D and bone mineral density and post-stroke hip fractures have been found in the long-term survivors of stroke.[18] Insufficient levels of vitamin D may not only impair bone mineralization but may also affect muscular function, increase bone loss via secondary hyperparathyroidism, may make the patient prone to frequent falls and recurrent hip fractures.[19]

To date, insignificant data is available in the Pakistani population that specifically highlights the association between vitamin D deficiency and stroke and this study was undertaken with the aim to generate a baseline data for a local population.

Rufin SD and colleagues found out that 52.94% of his stroke patients had a concomitant vitamin D deficiency[20] whereas Kuno H demonstrated low vitamin D levels in about 43% of the patients with stroke.[21] The results of both these studies are comparable and consistent with the findings of this study.

In a meta-analysis of a prospective study in a female population, Sun Q demonstrated a modest association between low vitamin D levels and the risk of stroke. It was also concluded that women who maintained adequate levels of vitamin D had a lower risk of stroke.[22]

Reports suggest that due to increased bone resorption in patients with stroke, there is resultant increased ionized calcium that suppresses PTH secretion, so the association between log 25(OH)D and log PTH was not observed in this group of stroke patients.[18]

Labelling vitamin D as a potential risk marker for stroke may warrant certain investigations because low vitamin D levels as in these studies may have preceded stroke. Secondly, hypertension occurring as a result of compensatory secondary hyperparathyroidism has been suggested as an attributable risk factor for stroke in patients with concomitant vitamin D insufficiency.[23]

Haroon Khan alongwith his colleagues conducted a study in a local population of Islamabad and its suburbs with the aim to determine the prevalence of existing vitamin D deficiency. It was recorded that vitamin D levels were significantly lower in females (56.2%) compared to males (15.3%).[16]

The high prevalence of vitamin D deficiency in females, especially those who stay indoors e.g., housewives involved in domestic work, may be due to inadequate exposure to sunlight. Also the religious, cultural and social norms of our society in which women wear clothes that almost completely cover their body may also prevent adequate sunlight exposure. Certain other factors that may also contribute to the prevailing vitamin D deficiency include overcooking of food and unawareness regarding the use of a healthy balanced diet. The Government needs to ensure complete support and commitment to launch public awareness campaigns

Conclusion

Vitamin D deficiency is significantly higher in stroke patients as compared to healthy controls. It is a potential risk marker for stroke, and the role of vitamin D repletion in enhancing musculoskeletal health after stroke needs to be explored and emphasized.

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