 DOI: 10.18231/2394-6377.2017.0038

Association of Vitamin D levels and Cognitive function in Postmenopausal women

R. Sudha[1,*], R. Kavitha[2], C. K. Vijayasamundeeswari[3]

[1,2]Assistant Professor, [3]Associate Professor, Dept. of Biochemistry, [1,3]Vinayaka Missions Kirupananda Variyar Medical College, Salem, Tamilnadu, Government Dharmapuri Medical college, Dharmapuri, Tamilnadu

***Corresponding Author:**
Email: sudhabharani76@yahoo.in

Abstract

Background: Vitamin D deficiency(VDD) is a major health concern in India, especially in elderly individuals and is adversely associated with neurocognitive function.

Aims and Objectives:

1. To assess the 25hydroxy vitamin D [25(OH)D] levels in postmenopausal women and compare it with premenopausal women.
2. To study the association of 25(OH)D levels with markers of cognitive impairment, that is Mini-Mental State examination(MMSE) and Addenbrooke's Cognitive Examination – Revised(ACE-R) score in postmenopausal women.

Materials and Method: A cross sectional study was conducted on 40 postmenopausal women and 40 premenopausal women as controls. The study subjects were analysed for 25(OH)D levels by ELISA and Cognitive function was assessed by using the MMSE and ACE-R score. Appropriate statistical analysis was done.

Results: Serum 25(OH)D levels (22.3±13.58 ng/ml Vs 32.4±12.4 ng/ml) in postmenopausal women were significantly lower (p-value = 0.03) when compared to the premenopausal women. A significant positive correlation was found between the 25(OH)D levels and the markers of cognitive decline (i.e) MMSE (r = 0.40) and ACE-R score (r = 0.61) in postmenopausal women. Even though the vitamin D levels in premenopausal women were higher than postmenopausal women, a significant proportion(60%) had vitamin D inadequacy.

Conclusion: A significantly lower 25(OH)D levels, MMSE and ACE-R scores were observed in postmenopausal women when compared to premenopausal women. 25(OH)D levels were significantly associated with markers of cognitive decline. These results suggest a potential role of Vitamin D in cognitive dysfunction in postmenopausal women and can be considered as an early marker for cognitive decline.

Keywords: Cognitive Function, Vitamin D, Postmenopausal Women, Neurocognitive Function.

Introduction

Vitamin D, popularly known as sunshine vitamin is both vital and indispensable for human beings. Vitamin D, a fat soluble steroid hormone is involved in numerous metabolic processes especially calcium and bone metabolism.[1] Despite abundant sunshine,Vitamin D deficiency is documented across all age groups and both sexes from India.[2] A study conducted in Delhi in healthy Indians above 50 years has reported that 91.2% subjects had VDD.[3] Vitamin D deficiency is not only related to fractures, but also increases the probability of stroke, diabetes and hypertension which leads to dementia[4-7] and may also be directly associated with the onset of neurodegenerative diseases.[8] Association of VDD with Cardiovascular diseases has been consistently proven globally.[9]

A growing body of evidence emphasizes the role of vitamin D in cognitive function[10-12] the results of which suggest that lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of Alzheimer's disease(AD).[12] More precisely, numerous preclinical and clinical studies suggest that hypovitaminosis D may be associated with increased risk of developing AD and dementia, without being a causal agent. Inducing genomic and non genomic effects, vitamin D plays a role on calcium homeostasis, neurotransmission, vascularization, Aβ and Tau accumulation, oxidative stress, and inflammation, all of which are disturbed in AD.[13]

Menopause is permanent cessation of menstruation following loss of ovarian activity, which has considerable impact on social, reproductive, physical and psychological health. Women in India are prone to an earlier menopause and all its implications on their health at an earlier age than their counterparts in the industrialized world.[14] Studies across the world have reported a high prevalence of Vitamin D deficiency in postmenopausal women.[15-18] Studies on postmenopausal women have also associated VDD with osteoporosis, obesity, cardiovascular risk and diabetes.[19] An observational study has reported that vitamin D deficiency was associated with increased risk of mortality, MI, HF or stroke in healthy postmenopausal women.[20] 82% of the postmenopausal women had varying degrees of low 25(OH)D levels in a study conducted in South India.[21]

As the role of vitamin D in skeletal health has been established, there is continued interest in vitamin D's broad spectrum of health benefits and outcomes. Although extensive research has been conducted on this arena, mixed results have been reported. Based on this background, our study analyzes the association of vitamin D levels with cognitive function in postmenopausal age group. Vitamin D's association with cognitive dysfunction in the postmenopausal women

may have significant implications in their health care, who are often the neglected part of the community.

Materials and Methods

The present cross sectional study was conducted over a period of 6 months from January 2015 to June 2015 at Vinayaka Missions Kirupananda Variyar Medical College. After obtaining the Institutional Ethical Committee clearance and informed consent from the patients, the study was initiated. A total of 80 women were considered for the study which includes 40 post menopausal women and 40 premenopausal women attending the Gynaecology Out Patient Department. Postmenopausal status is defined as cessation of menstruation for atleast one year. Those women who were on drugs like oral contraceptives, statins, anticonvulsants, vitamin D or calcium supplementations and women with endocrine disorders, chronic liver or kidney disease were excluded.

Demographic and anthropometric data were collected from all the women. Body mass index (BMI), Waist Hip ratio (WHR) and blood pressure (BP) were recorded. All the women answered a questionnaire assessing the cognitive function by Mini-Mental State examination (MMSE) and Addenbrooke's Cognitive Examination – Revised (ACE-R) score.

In MMSE, functions such as registration, attention, calculation, recall, language (comprehension, reading, writing and naming), ability to follow simple commands, and orientation were examined. For MMSE, scores above 27 are considered normal and scores below 24 indicates impairment in cognition.[22] The ACE-R is a brief cognitive test that assesses five cognitive domains, namely attention/ orientation, memory, verbal fluency, language and visuospatial abilities. Total score is 100, higher scores indicates better cognitive functioning. Administration of the ACE-R takes, on average, 15 minutes. ACE scores 90 or above indicates normal cognition and scores below 90 indicates cognitive impairment.[23] ACE–R accomplishes standards of a valid dementia screening test, sensitive to early cognitive dysfunction.

Venous blood samples were collected in the morning after an overnight fast of 8-12 hours. Fasting blood glucose (FBG), triglycerides (TG), Total cholesterol (TC), HDL-cholesterol were analysed by Glucose oxidase peroxidase, Glycerol oxidase peroxidase, Cholesterol oxidase peroxidase and Direct method respectively. LDL-cholesterol levels were calculated by Friedwald formula. Serum 25-(OH) vitamin D was estimated by Enzyme linked immunosorbent assay(ELISA). Measurement of 25(OH)D in the circulation is the best diagnostic test to determine the vitamin D status of a person. Several Indian studies have used the following cut off levels for VDD. The vitamin D levels are considered normal when it is >30ngms/ml, and it is insufficient when the level is between 20 – 30ngms/ml and deficit when it is less than 20ngms/ml.[20]

Statistical Analysis: Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) software. Values were expressed as Mean ± Standard deviation. Student's t-test was used to compare the postmenopausal group with the premenopausal group. Correlation between two variables was assessed by using the Pearson's correlation coefficient. A p-value of <0.05 was considered as statistically significant.

Results

A total of 80 women were studied in this cross sectional study. The women were categorized into 2 groups, premenopausal and postmenopausal group. Table 1 shows the demographic and anthropometric details of the study subjects. Table 2 shows the markers of cognitive function in pre and postmenopausal women. The markers of cognitive function were significantly decreased in postmenopausal women.As shown in Table 3, vitamin D levels were significantly low in postmenopausal women when compared to the premenopausal women. Table 4 depicts the correlation of Vitamin D levels with the MMSE and ACE-R scores in which a positive correlation was noted between them in postmenopausal women.

Table 1: General characteristics of study subjects

Variable	Post-menopausal women (M±SD)	Pre-menopausal women (M±SD)	P-value
Number(n)	40	40	
Age (yrs)	59.71 ± 5.27	40.84 ± 2.24	
BMI	29.9 ± 2.42	24.5 ± 3.33	0.032*
WHR	0.84 ± 0.03	0.78 ± 0.04	6.24

BMI – Body Mass Index, WHR – Waist Hip Ratio, *statistically significant

Table 2: Markers of cognitive function in study subjects

Variable	Post-menopausal women (M±SD)	Pre-menopausal women (M±SD)	P-value
MMSE	21.6 ± 4.97	25.42 ± 1.65	0.01*
ACE-R	78.65 ± 11.02	83.11 ± 5.63	0.04*

MMSE - Mini-Mental State examination, ACE-R - Addenbrooke's Cognitive Examination – Revised score *statistically significant

Table 3: Laboratory data of study subjects

Parameter	Post-menopausal women (M±SD)	Pre-menopausal women (M±SD)	P-value
Vitamin D (ng/ml)	22.3±13.58	32.4±12.4	0.03*

Total cholesterol (mg/dl)	213.03±47.01	157.17±7.01	0.0001*
Triglycerides (mg/dl)	179.37±8.96	159.80±54.9	0.18
HDL(mg/dl)	47.57±4.32	47.07±5.65	0.7
LDL(mg/dl)	85.57±29.34	74.33±37.91	0.20

*statistically significant

Table 4: Correlation of Vitamin D levels with markers of cognitive decline

Variable	r-value	p-value
MMSE	0.40	<0.01
ACE-R	0.61	<0.001

Discussion

Serum 25(OH)D is the major circulating metabolite of vitamin D and reflects vitamin D inputs from cutaneous synthesis and dietary intake. The serum 25(OH)D level is a widely used and standard clinical measure of vitamin D status. Wide spread VDD has been recognized in Indians of all age groups with the highest prevalence in older age groups. Hypovitaminosis D is nearly universal above the age of 50 years in northern part of India.[3] We found a high prevalence of VDD in postmenopausal women (73%) which is in accordance with many other studies.[15-19] One of the highest prevalence among postmenopausal women above 50years have been from Croatia and France where 92.5% and 89.9% had vitamin D insufficiency.[24,25]

A significant proportion(60%) of premenopausal women were also having inadequate levels of vitamin D. While analyzing the cardiometabolic risk profile in the two groups, only BMI and total cholesterol were significantly high in the postmenopausal group. Postmenopausal period is associated with an increased risk of obesity and a shift to an abdominal fat distribution with associated increase in health risks. Many investigators have associated Vitamin D deficiency and increased cardiometabolic risk. Yet a recent study conducted at a teaching hospital in India states that there is no correlation of serum vitamin D concentrations with cardiometabolic risk factors.[26]

Age is a crucial factor in determining the levels of vitamin D. Cutaneous synthesis of vitamin D is influenced by ageing which affects multiple steps of vitamin D metabolism.VDD is common in elderly due to limited sunlight exposure, decreased 7-dehydrocholesterol in the skin, as well as ageing skin has reduced efficiency to absorb sunlight and synthesize the required amount of vitamin D. Other factors precipitating VDD in the elderly are inadequate dietary vitamin D intake, and limited physical activity which are common in elderly rural women. So, postmenopausal women are more vulnerable to vitamin D deficiency, owing to their inevitable ageing process coupled with obesity.

The MMSE and ACE scores aid in understanding cognitive status of individual, and thus in the diagnosis of Cognitive decline.[22,23] Markers of cognitive dysfunction were significantly decreased in postmenopausal women when compared to the premenopausal women. Also, our observations show a significant positive correlation of 25(OH)D levels with the MMSE and ACE-R scores. This is in agreement with Yelena Slinin et al,[10] where very low 25(OH)D levels among older women were associated with higher odds of global cognitive impairment. Other studies which have found an association with vitamin D levels and risk of cognitive decline are Tejal Kanhaiya Vedak et al,[11] Llewellyn et al,[27] Babak Hooshmand et al,[28] CL Chei et al.[29]

Several mechanisms have been suggested linking the role of vitamin D and risk of cognitive dysfunction. The active form vitamin D is a seco-steroid with multiple neurotrophic and neuroprotective functions in the central nervous system. Vitamin D plays a pivotal role in the development of brain as well as in adult brain function. All the cell types within the brain have the ability to synthesize active vitamin D. Both the vitamin D receptor and the enzyme required for the synthesis of active vitamin D are found in the adult human brain. At the molecular level, the brain has the ability to synthesize the active form of vitamin D within many cell types and regions with predominance in the hypothalamus and the large neurons within the substantia nigra.[30] Vitamin D contributes to neuroprotection by modulating the production of nerve growth factor (NGF), neurotrophin, glialcell-derived neurotrophic factor (GDNF), nitric oxide synthase(NOS), and choline acetyltransferase.[12]

Strength of this study is that, it is done at an earlier stage before the onset of cognitive dysfunction. Quality of life of postmenopausal women can be improved when VDD can be timely prevented, early diagnosed and adequately managed.

Limitations

The study was a cross sectional study with small sample size. The study is also based only on a single measurement of Vitamin D and it would have been ideal if follow up studies were done and also, calcium and parathyroid hormone levels were evaluated.

Conclusion

These results suggest a potential role of Vitamin D in cognitive dysfunction in postmenopausal women suggesting vitamin D as an early marker for cognitive decline.These findings may be helpful in designing the preventive measures of cognitive dysfunction in postmenopausal women who often seek health care rarely.

References

1. Hector F DeLuca. Overview of general physiologic features and functions of vitamin D. AmericanJournal ofClinical Nutrition. 2004;80(suppl):1689S–96S.

2. Harinarayanan CV, Shashank R.Joshi. Vitamin D status in India – Its implications and remedial measures. Journal of Association of Physicians of India.2009;57:40-48.
3. RK Marwaha, Tandon N, Garg MK, Ratnesh Kanwar, A Narang, A Sastry, et al. Vitamin D Status in Healthy Indians Aged 50 Years and Above. Journal of Association of Physicians of India..2011;59:706-709.
4. Schottker B, Herder C, Rothenbacher D, Perna L, Müller H, Brenner H. Serum 25 hydroxyvitamin D levels and incident diabetes mellitus type 2: A competing risk analysis in a large population-based cohort of older adults. Eur J Epidemiol. 2013;28:267-275.
5. Forman JP, Bischoff-Ferrari HA, Aollett WC, Stampfer MJ, Curhan GC. Vitamin D intake and risk of incident hypertension:Results from three large prospective cohort studies. Hypertension. 2005;46:676-682.
6. Sun Q, Pan A, Hu FB,Manson JE, Rexrode KM. 25-hydroxy vitamin D levels and the risk of stroke:A prospective study and meta analysis. Stroke. 2012;43:1470-1477.
7. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med.2012;2(8).
8. Dickens AP, Lang IA, Langa KM, Kos K, Llewellyn DJ. Vitamin D, cognitive dysfunction, and dementia in older adults. CNS drugs.2011;25:629-639.
9. Biswajit Das, Trinath Kumar Mishra, Satya Narayan Routray, Chhabi Satpathy, Hrudananda Mishra. Vitamin D deficiency: A new risk factor for cardiovascular disease JIACM 2013;14(3-4):247-52.
10. Slinin, Y., Paudel, M., Taylor, B. C., Ishani, A., Rossom, R., Yaffe, K., et al. Association Between Serum 25(OH) Vitamin D and the Risk of Cognitive Decline in Older Women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2012;67(10),1092–1098.
11. Vedak, T. K., Ganwir, V., Shah, A. B., Pinto, C., Lele, V. R., Subramanyam, A., et al. Vitamin D as a marker of cognitive decline in elderly Indian population. Annals of Indian Academy of Neurology. 2015;18(3),314–319.
12. Balion, C., Griffith, L. E., Strifler, L., Henderson, M., Patterson, C., Heckman, G., et al. Vitamin D, cognition, and dementia: A systematic review and meta-analysis. Neurology. September 2012;79(13),1397–1405.
13. Verena Landel, Cedric Annweiler, Pascal Millet, Maria Morello, Francois Feron. Vitamin D, Cognition and Alzheimer's disease. The therapeutic benefit is in the D-tails. Journal of Alzheimer's disease. 2016;53:419-444.
14. Alka Kriplani, Kaberi Banerjee. An overview of age of onset of menopause in northern India. Maturitas. 2005;52(3-4):199-204.
15. Gaugris S, Heaney RP, Boonen S, Kurth H, Bentkover JD, Sen SS. Vitamin D inadequacy among postmenopausal women: A systematic review. QJM.2005;98(9):667-76.
16. Lim SK, Kung AW, Sompongse S, Soontrapa S, Tsai KS. Vitamin D inadequacy in postmenopausal women in Eastern asia. Curr Med Res Opin. 2008;24(1):99-106.
17. Agarwal N, Mithal A, Kaur P, Dhingra V, Godbole MM, Shukla M. Vitamin D and insulin resistance in postmenopusal Indian women. Indian J Endocrin Metab. 2014;18(1):89-93.
18. Tandon VR, Sharma S, Mahajan S, Raina K, Mahajan A, Khajuria V et al. prevalence of vitamin D deficiency among Indian postmenopausal women and its correlation with diabetes:A first Indian crosssectional data. J Mid – Life Health. 2014;5(3):121-125.
19. Holick MF. Vitamin D Deficiency. N Engl J Med 2007;357:266-81.
20. Louise Lind Schierbeck, Lars Rejnmark, Charlotte Landbo Tofteng, Lis Stilgren,----- Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events: a 16-year follow-up study, European Journal of Endocrinology. 2012;167:553–560.
21. Harinarayanan CV. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. Osteoporosis Int. 2005 Apr;16(4):397-402.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res. 1975;12:189-198.
23. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening, International Journal of Geriatric Psychiatry. 2006;21(11):1078-85.
24. Laktasic-Zerjavic N, Korsic M, Crncevic-Orlic Z, Kovac Z, Polasek O, Soldo-Juresa D. Vitamin D status, dependence on age, and seasonal variations in the concentration of vitamin D in Croatian postmenopausal women initially screened for osteoporosis. Clin rheumatol 2010;29(8):861-7.
25. De Cock C, Bruyere O, Collete J, Reginster JY. Vitamin D inadequacy in French osteoporotic and osteopenic women. Joint Bone Spine 2008;75:567-72.
26. Mitra S, Nayak PK, Agrawal S, Sahoo JP, Kamalanathan S, Nanda R. Vitamin D Status and Cardio-Metabolic Risk in Indian Postmenopausal Women. Journal of Clinical and Diagnostic Research. 2016;10(3):QC17-QC20.
27. Llewellyn DJ, Lang IA, Langa KM, et al. Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med. 2010;170:1135-1141.
28. Babak Hooshmand, Johan Lokk, Alina Solomon, Franscesca Mangialasche, Julia Miralbell, Gabriella Apilber et al. Vitamin D in Relation to Cognitive impairment, cerebrospinal fluid biomarkers, and brain volumes. Journals of Gerontology: Medical Sciences. 2014;69(9):1132-1138.
29. Choy-Lye Chei, Prassanna Raman, Zhao-Xue Yin, Xiao-Ming Shi, Yi Zeng, David B.Matchar. Vitamin D levels and cognition in the elderly population in China. J Am Geriatr Soc. 2014;62(11):2125-2129.
30. 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.