Relationship between Level of 25 (OH) D Vitamins and Cognitive Impairment in Chronic Kidney Disease (CKD) in Dialysis and Non-Dialysis Patients Using Trial Making Test B

Alaa Abdlhussein Abdulzahra[1], Adel Sahip Al-Mayaly[2], Foaad Kadhim Shaghee[3], Widad Mohammed Mousa[4]

[1,3]Department of Internal Medicine, Faculty of Medicine, Jabir Ibn Hayyan Medical University, Najaf, Iraq. [2]Department of Surgery, Faculty of Medicine, Jabir Ibn Hayyan Medical University, Najaf, Iraq. [4]Department of radiology, Al-Sadr Teaching hospital, Al-Najaf Health Directory , Najaf , Iraq. Corresponding author: Assist. Prof. Dr. Alaa Abdlhussein Abdulzahra, dr.alaa828@yahoo.com

ABSTRACT

Deficiency in vitamin D and cognitive dysfunction commonly are associated together in patients suffering from chronic kidney disease (CKD) in both dialysis and non-dialysis patients, vitamin D develop new protective regulatory roles in the functions of CNS. Combination of low levels of vitamin D and CKD can be enrolled for devastating and lead to sever cognitive dysfunction. Patients with CKD mostly associated with Hypovitaminosisand moreover common in elderly patients and related with cognitive decline, one of the hypotheses that CKD patients commonly have a low level of vitamin D and have potential experience in accelerated cognitive decline which rarely link on this topic. Most of CKD patients particularly sensitive for developing in the deficiency of vitamin D. Reduce vitamin D intake, male absorption in compromised GIT patients, loosing of vitamin D binding protein with urine, and α-hydroxylase enzyme reduction in the kidney all are the risk factors included in the causes of 25(OH) D vitamin decrease production.

Aim of study: assess cognitive function by using one validated score: trial making test B in patients with CKD in both dialysis and non-dialysis.

Patients and methods: a total of 54 patients with CKD and 57 patients with ESRD on hemodialysis enrolled in this study, where CKD defined as GFR < 60 ml/min by MDRD study. Exclusion criteria include CVA, deaf and blind, and low education patients. Cognitive functions assessment done for patients who are on hemodialysis and non- dialysis by using trial B testing, this second assess spatial scanning concentration and executive function by time measuring that needed to connect the series of numbered that are sequentially and littered circles. Catastrophic shorter time completion with a maximum of 300 second indicates better performance. 25 (OH) D vitamins has assessed from each patients using direct immunoassay method, with assay at 4-110 ng/ml.

Results: for patients on hemodialysis 27 (39.7%) has deficient 25(OH) D vitamin status 25 (36.7%) insufficient,20 (29.4%) had sufficient vitamin D levels, significant low level in patients on hemodialysis in comparison to those with non-hemodialysis. Trial making test B score was significantly lower in dialysis patients, significant correlation between cognitive function assessment (trial making test B) and low vitamin D level.

Conclusions: the prevalence of deficiency in vitamin D in CKD especially hemodialysis patients associated with cognitive decline.

Keywords: CKD, ESRD, dialysis, vitamin 25(OH) D, and trial making test B.

Introduction

Cognitive impairment (CI) and deficiency in vitamin D always together detected in CKD patients. Meanwhile in CNS regulatory and neuroprotective roles were played by vitamin 25(OH) D. These factors draining are effective clues lead to CI and complicate through related processes which important causes for mortality in addition to morbidity. Deficiency in vitamin D and cognitive decline have both together important effect on CKD patients, where the periodical determination of status of D vitamin and its supplementation, with continuous screening for neuropsychological state must be achieved in of clinical care units for CKD patients [1].Cognitive impairment have been accelerated with deficiency of vitamin D in CKD patients, in spite of this fact little previous studies achieved in this side[2]. The sources of vitamin D are photosynthesis, vitamin enriched diet, and oral supplementation with tow formula one is 25(OH)D and the other 1,25(OH)2D where the second one is the active form which derived from1α-hydroxylation of the first form where occur in kidney and other tissues like brain[3]. Other function of vitamin D is to regulate the levels of phosphorous and calcium and keeping the bones healthy[4, 5, 6, 7]. All ages are affected by deficiency in the level vitamin D and consider a risk factor resulted from CKD, deficiency of sun exposure, obesity, and inadequate diet[8]. Pollutions of the air is a risk factor for deficiency of vitamin D according to low level of UV light[9]. Level of vitamin D also affected by genetic variation within populations according to changes in polymorphism of 1α-hydroxylase enzyme and expression of vitamin D binding protein[10-13], So that this study was aimed to assess cognitive function by using one validated score: trial making test B in patients with CKD in both dialysis and non-dialysis.

Patients and methods

The study archived in the campus of Baghdad Medical city; the study extended during the period from May 2019 to February 2020. Hemodialysis center received ESRD patients three times weekly, with period of 3-4 hours for each treatment. A trained nephrologists screened all the participants, and assess their eligibility criteria for CKD, in which CKD was defined as eGFR<60 mL/min on at least two occasions during the period of study (calculated using six-variable in the Modification of Diet in Renal Disease (MDRD) study). In ESRD patients the recording of laboratory data occurs periodically in each month, And the values of cognitive function testing recorded within 1 month (parameters other than cholesterol and parathyroid hormone recorded within 6 months)

***Trail making Test B (Trails B)*[14]:** Visuospatial scanning, executive function (duties which in need for self-shifting and memory) were evaluated by this test as well as to concentration, all that values used to estimate the time required to link sequential series of lettered and numbers circles. Better performance indicated by completion within short time out of 300 second maximum.

***Cognitive impairment* [15]:** Consistent with prior studies, the function that is impaired executive considered to be a Trails B score of > 300 sec.

Vitamin D assessment: Vitamin D [25(OH) D] levels assessed from each participant, using a direct enzyme immunoassay method [16]. With assay range 4.0 – 110 ng/mL (product code: IS-2520N).

Statistical analysis: For comparison between two categorical variable chi-square tests used, while for two continuous independent t-tests used. Linear regression analysis used for assessment of the correlation between vitamin D or serum creatinine with cognitive function score. All analyses carried out using SPSS version 23.1, p-value considered to be significant <0.05.

Results

A total of 63 CKD and 68 patients with ESRD for dialysis that enrolled in present study, for assessment of the baseline no significantly differences in age, gender, hypertension history, and the coronary artery disease (CAD), accordingly the history of diabetic, and serum creatinine was significant higher in patients on dialysis, while serum hemoglobin was significantly lower in dialysis patients compared to CKD patients as illustrated in table 1.

Table 1: Baseline characteristics

Variables		CKD	Dialysis	p-value
Number		63	68	-
Age (y), mean ± SD		49.0 ± 9.5	52.0 ± 9.1	0.457
Gender, n (%)	Female	26 (41.3%)	31 (45.5%)	0.755
	Male	37 (58.7%)	37 (54.4%)	
Diabetic, n (%)		29 (46.0%)	40 (58.8%)	0.019
Hypertension, n (%)		55 (87.3%)	59 (86.8%)	0.322
CAD, n (%)		28 (44.4%)	27 (39.7%)	0.780
GFR		32.9 ± 9.7	-	-
Creatinine (mg/dL), mean ± SD		3.2 ± 1.1	8.7 ± 2.7	<0.001
Hemoglobin (mg/dL), mean ± SD		9.8 ± 1.3	7.8 ± 0.7	<0.001

For CKD patients, 27.0 ± 6.7 had deficient 25 (OH) D levels, 40.4% insufficient, while 0 (0%) had sufficient levels of 25 (OH) D levels. According to vitamin D levels in patients with dialysis only 27 (39.7%) had sufficient amount level, while 25 (36.7%) deficient level of vitamin and only 20 (29.4%) recorded in serum level ≥20 ng/mL, serum had significant level of 25 (OH) vitamin D lower in patients on dialysis compared to those with CKD, as illustrated in table 2.

Table 2: Assessment of vitamin D

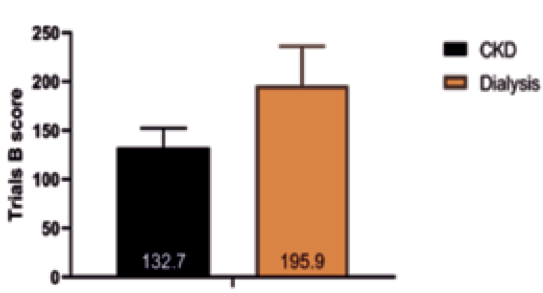
Variables	CKD	Dialysis	p-value
Number	63	68	-
25 (OH)D (ng/mL), mean ± SD	27.0 ± 6.7	15.7 ± 5.3	<0.001
<12 ng/mL	0 (0%)	27 (39.7%)	
12 – <20 ng/mL	23 (36.5%)	25 (36.7%)	
≥20 ng/mL	39 (61.9%)	20 (29.4%)	

Mean Trails B was higher significantly in dialysis patients compared with CKD, as illustrated in table 3 and figure 1.

Table 3: Numbers and Mean of Tests on Performance and Reports of Self- Questionnaire for Subjects withESRDand CKD

Variables	CKD	Dialysis	p-value
Number	63	68	-
Trails B	132.7 ± 19.6	195.9 ± 40.5	<0.001
Trails B, lower scores indicate better performance.			

Figure 1: assessment of trials B score

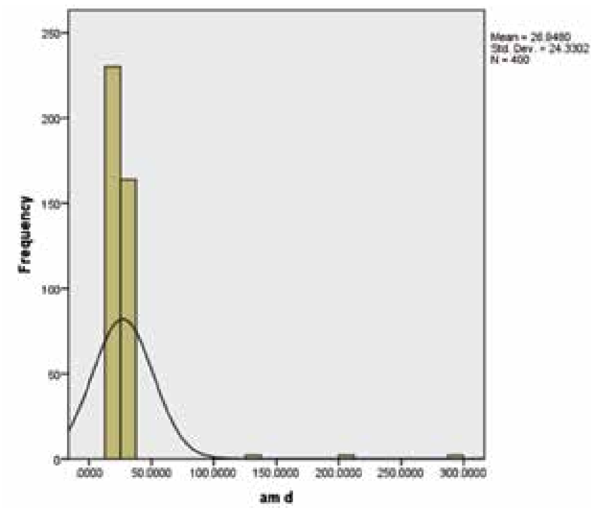


There was a significant correlation between various cognitive function tests (Trials B) with vitamin D, as illustrated in table 4 and figure 2.

Table 4: The relationship between 25 (OH) D with various cognitive functions in dialysis patients

	25 (OH) D	
	r	p-value
Trails B	-0.890	<0.001
r: correlation coefficient		

Figure 2: relationship between vitamin D with trials B score in dialysis patients



There was a significant correlation between various cognitive function tests (Trials B) with creatinine, as illustrated in table 5.

Table 5: Relationship between serum creatinine with various cognitive functions in dialysis patients

	Creatinine	
	r	p-value
Trails B	0.833	<0.001
r: correlation coefficient		

Discussion

In our study, the mean age patients was (52.0 ± 9.1) years for dialysis patients and (49.0 ± 9.5) years for CKD patients, which related to other studies like, Jovanovich et al (a study carried out in the USA involved 247 CKD patients, 358 ESRD on dialysis patients) mean age was 69 ± 12 years for CKD patients and 66 ± 11 years for ESRD patients [17], Liu et al study (study carried out in China involved 273 peritoneal dialysis patients) mean age was similar to our 53.58 ± 14.06 years [18]. In the present study, there was a direct significant correlation between serum creatinine with Trails B score. This indicates poor cognitive function associated with lower creatinine in ESRD patients on dialysis. In our study the correlation was significant between 25 (OH) D and Trails B score (r = -0.890, p-value < 0.001).Other study for 858 elderly Italian patients more than 65 years old were the relative risk was significantly higher cognitive decline in patient with level lower than 10 ng/ml of vitamin D, associated with patients higher than 30ng/ml of vitamin over period of 6-years [19, 20]. The European men for elderly people is less than 14 ng/ml which mostly related to low performance on tests which evaluated the rapidity of information processes but not memory [21]. Mechanisms by which vitamin D related to CI are more varies, in one study 255 U.S. patients with hemodialysis by mean of 62.9 ± 16.9 over the period of 2004-2012, reported that 139(49%) of patients had level of vitamin D between 12-20 ng/ml, and 36(14%) had level lower than 12 ng/ml, while 80(31%) recorded more than 20 ng/ml[22]. The higher global cognitive score is associated independently with level lower higher than 20 ng/ml of vitamin D, while lower levels are related to impaired executive function nevertheless not for global function[23, 24, 25, 26].Study include 36 patients in the Veterans Affairs Medical Centers between 2001-2006, all with CKD patients with dialysis and non-dialysis the result show that there is no relationship for level of vitamin D with cognitive function[17]. Conversely, vitamin D levels in the blood measured between 2002 and 2004, years before processing cognitive tests in 2005-2006, the result not completely explain there is an effect on cognitive study period by the level of vitamin D, and still remain the same level with first period of study. Within phone calls for 20 min the test done, and lead to selection bias. The result shows that most of the patients had not well physically feeling, with several point of cognitive impairment; they were having no tolerance a conversation in the phone for 20 minutes. This type of patients not involved in the current study. Then the selection of patients could be directed toward null hypothesis and healthier patient population. This study used to a different battery of instruments for cognitive capacity measuring. Therefore, it is not fair to equate current study with the studies of Shaffi et al, and Liu et al. [18, 22].

Conclusions

revalence of vitamin 25 (OH) D deficiencies in CKD especially cognitive decline associated with hemodialysis patients

References

1. Cheng Z, Lin J, Qian Q. Role of Vitamin D in Cognitive Function in Chronic Kidney Disease. Nutrients. 2016;8(5):291.
2. Holick MF. Vitamin D deficiency. The New England journal of medicine. 2007;357(3):266-81.
3. Jones G. Expanding role for vitamin D in chronic kidney disease: importance of blood 25-OH-D levels and extra-renal 1alpha-hydroxylase in the classical and nonclassical actions of 1alpha,25-dihydroxyvitamin D(3). Seminars in dialysis. 2007;20(4):316-24.
4. Lowry MB, Guo C, Borregaard N, Gombart AF. Regulation of the human cathelicidin antimicrobial peptide gene by 1α,25-dihydroxyvitamin D3 in primary immune cells. The Journal of steroid biochemistry and molecular biology. 2014;143:183-91.
5. Heaney RP. Vitamin D in health and disease. Clinical journal of the American Society of Nephrology: CJASN. 2008;3(5):1535-41.
6. Chen G-C, Zhang Z-L, Wan Z, Wang L, Weber P, Eggersdorfer M, et al. Circulating 25-hydroxyvitamin D and risk of lung cancer: a dose-response meta-analysis. Cancer causes & control : CCC. 2015;26(12):1719-28.
7. Hollis BW. Assessment of vitamin D status and definition of a normal circulating range of 25-hydroxyvitamin D.

Curr Opin Endocrinol Diabetes Obes. 2008;15(6):489-94.
8. Bassil D, Rahme M, Hoteit M, Fuleihan GE-H. Hypovitaminosis D in the Middle East and North Africa: Prevalence, risk factors and impact on outcomes. Dermato-endocrinology. 2013;5(2):274-98.
9. Calderón-Garcidueñas L, Franco-Lira M, D'Angiulli A, Rodríguez-Díaz J, Blaurock-Busch E, Busch Y, et al. Mexico City normal weight children exposed to high concentrations of ambient PM2.5 show high blood leptin and endothelin-1, vitamin D deficiency, and food reward hormone dysregulation versus low pollution controls. Relevance for obesity and Alzheimer disease. Environmental research. 2015;140:579-92.
10. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. The American journal of clinical nutrition. 2012;95(1):91-100.
11. Chonchol M, Kendrick J, Targher G. Extra-skeletal effects of vitamin D deficiency in chronic kidney disease. Ann Med. 2011;43(4):273-82.
12. Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ (Clinical research ed). 2014;348:g1903-g.
13. Arabi A, El Rassi R, El-Hajj Fuleihan G. Hypovitaminosis D in developing countries-prevalence, risk factors and outcomes. Nature reviews Endocrinology. 2010;6(10):550-61.
14. Yeudall LT, Reddon JR, Gill DM, Stefanyk WO. Normative data for the Halstead-Reitan neuropsychological tests stratified by age and sex. Journal of Clinical Psychology. 1987;43(3):346-67.
15. Ebly EM, Hogan DB, Parhad IM. Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. Arch Neurol. 1995;52(6):612-9.
16. IDS PLC—A-Z List of Products. Available at: https://www.idsplc.com/products/25-vitds/ Accessed January, 2020.
17. Jovanovich AJ, Chonchol M, Brady CB, Kaufman JD, Kendrick J, Cheung AK, et al. 25-vitamin D, 1,25-vitamin D, parathyroid hormone, fibroblast growth factor-23 and cognitive function in men with advanced CKD: a veteran population. Clin Nephrol. 2014;82(5):S1-S4.
18. Liu G-L, Pi H-C, Hao L, Li D-D, Wu Y-G, Dong J. Vitamin D Status Is an Independent Risk Factor for Global Cognitive Impairment in Peritoneal Dialysis Patients. PloS one. 2015;10(12):e0143782-e.
19. Llewellyn DJ, Lang IA, Langa KM, Muniz-Terrera G, Phillips CL, Cherubini A, et al. Vitamin D and risk of cognitive decline in elderly persons. Archives of internal medicine. 2010;170(13):1135-41.
20. Miller JW, Harvey DJ, Beckett LA, Green R, Farias ST, Reed BR, et al. Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults. JAMA Neurol. 2015;72(11):1295-303.
21. Lee DM, Tajar A, Ulubaev A, Pendleton N, O'Neill TW, O'Connor DB, et al. Association between 25-hydroxyvitamin D levels and cognitive performance in middle-aged and older European men. Journal of neurology, neurosurgery, and psychiatry. 2009;80(7):722-9.
22. Shaffi K, Tighiouart H, Scott T, Lou K, Drew D, Weiner D, et al. Low 25-hydroxyvitamin D levels and cognitive impairment in hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN. 2013;8(6):979-86.
23. Vaidya A, Forman JP. Vitamin D and vascular disease: the current and future status of vitamin D therapy in hypertension and kidney disease. Curr Hypertens Rep. 2012;14(2):111-9.
24. Lee SY, Kim HY, Gu SW, Kim HJ, Yang DH. 25-Hydroxyvitamin D Levels and Vascular Calcification in Predialysis and Dialysis Patients with Chronic Kidney Disease. Kidney and Blood Pressure Research. 2012;35(5):349-54.
25. Assimon MM, Salenger PV, El-Fawal

HA, Mason DL. Nutritional vitamin D supplementation in haemodialysis: A potential vascular benefit? Nephrology (Carlton, Vic). 2012;17(3):237-42.
26. Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, Porter NM. Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2001;21(1):98-108.