Low Vitamin D Level and Its Relation to Cognitive Function in Chronic Kidney Diseases (Dialysis and Non-Dialysis) Patients

Alaa Abdlhussein Abdulzahra1*, Ali Jasim Hasim Al Saedi2

1Department of Internal Medicine, Faculty of Medicine, Jabir Ibn Hayyan Medical University, Najaf, Iraq
2Head Professor of Nephrology and Renal Transplantation, MD FACP FRCP Edin, College of medicine, Baghdad University, Baghdad, Iraq

*Corresponding author: Prof. Dr. Alaa Abdlhussein Abdulzahra, Email: dr.alaa828@yahoo.com

Abstract
Cognitive disability and vitamin D deficiency are mostly common in chronic kidney disease (CKD) patients. Vitamin D applies protective and controlling role in the CNS. Low level of D vitamin has been related with the weakness of muscle and bone trouble, circulatory disorders (hyperlipidemic, diabetes, and hypertension), oxidative injury, infections, immune decline and neurocognitive impedance. The level of vitamin D that is suboptimal is very common as well as to CKD. The two disorders, especially predominant in patients older than 65 years, and are known dangers for firmly connected with cognitive impairment. In spite of the fact that it is estimated that patients with CKD insufficient vitamin D level might encounter a quickened cognitive decline, and just little effectively planned studies achieved in this subject. Aim of study: Assessment of cognitive function in association with vitamin D level in patients with CKD with or without dialysis. Patients and methods: the study include two groups; 61 dialysis and 56 CKD nondialysis patients enrolled in our study, in which CKD was defined as eGFR <60 mL/min on at least two occasions during the previous study period (calculated using Modification of Diet in Renal Disease (MDRD) study). The exclusion criteria are: patients below 20 years old, pregnant ladies, deaf, blind and patients with stroke. The cognitive function had been assessed by using 1- The Mini-Mental State Examination (MMS) to assess ‘attention, short term and immediate recall and language2- Trail making Test B (Trails B) estimating the time needed to associate progression at succession numbered and lettered circles. Vitamin D assessed by using direct enzyme immune assay method.

Results: For dialysis patients, 39.3 % had deficient 25(OH) D levels, 34.4 % insufficient, 24.5 % had sufficient 25(OH) D levels. Serum 25 (OH) vitamin D was significantly lower in dialysis patients compared to those with CKD, Mean MMs score was significantly lower in dialysis patients compared to CKD, while Trail B was significantly higher in dialysis patients. There was a significant correlation between various cognitive function tests (MMs, and Trials B) with vitamin D, There was a significant relation between various cognitive capacity tests (MMs, and Trials B) with creatinine. Conclusion: There is a high incidence of low 25(OH)D level in patients with CKD especially those on hemodialysis and that deficiency in vitamin D may be related to poor cognitive capacity.

Keywords: CKD, ESRD, minimal status domain, and 25(OH)D-level

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Introduction
Normally Vitamin D obtained through eating routine, photosynthesis, and by supplementary products. Two types of D vitamin available for use: the first one is 25(OH) D and the second type 1, 25(OH) 2D, while the 1, 25(OH) 2D is the most active structure, created through 1α-hydroxylationfrom 25(OH) D. The hydroxylation happens mainly in the kidney yet in addition in different tissues like CNS (1).Patients with CKD especially vulnerable to the developing deficiency in the D vitamin. The hazard components may be resulted from diminished intake of vitamin D, decrease bowel absorption, low level of vitamin D bounded protein, decrease in the intra-renal action of 1α-hydroxylase lead to deficient 1,25(OH)3D production, and rise in fibrotic growth factor 23 (FGF-23), that prevent 1α-hydroxylase action. CKD patients frequently had some of extra comorbidties (hypertension, obesity, diabetes, and older ages) considered as increasing chance elements to vitamin D lacking (2). Developing evidence recommends a significant role for vitamin D in physiology of CNS and can transported throw the blood-brain barrier in the vessels of cerebrum and enters the brain within the fluids of cerebrospinal by passive distribution and specific transporters. The quantity in cerebrospinal fluid of 25(OH) D is firmly associated with serum quantity. Vitamin D applies its activities through VDR, which is

presented in glial cells and neurons in practically all areas of the CNS. Specifically, the VDR is communicated in the sub cortex area, cortex, hypothalamus, hippocampus, and, the regions important for cognition \(^{(3)}\). The CKD populace, particularly older CKD, is increasingly. CI among this part of the populace has now been progressively recognized. An across the country test for community of U.S. staying adults (age more than 45 years), urine protein elimination and eGFR decline were strongly related connecting with CI \(^{(4)}\).

### Patients and methods

The study was carried out in Baghdad Medical city campus (tertiary referral center), the study carried out during the period from April 2019 till the end of January 2020, ESRD patients got in hemodialysis center for three times each week, and for 3 to 4 hours for each management, using low-flux polysulfide dialyzers and ultra filtration-controlled machines.

### Participants

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 previous study period (calculated using Modification of Diet in Renal Disease (MDRD) study) \(^{(5)}\). The following subjects were excluded from the study; patients below 20 years old, pregnant ladies, deaf , blind and patients with stroke.

### Variables

Demographic, clinical data, and cognitive test were collected from all patients, cognitive tests were administered during the hemodialysis treatment (staying away from the start or end of treatment) to limit the impacts of variances in effects or BP. For CKD patients, the examinations were performed after a visit of clinic. Patients interview during the 1st hour of dialysis for HD group, and at a regular visit of CKD patients. Drug use, like the utilization of narcotics, benzodiazepines, antidepressants, lipid-lowering medication, antihypertensive drugs, was recorded for all patients in this study. For ESRD patients, laboratory readings on the end of months were documented. For CKD patients, laboratory values taken within one month of cognitive domain testing have been recorded (except for parathyroid hormone and lipid, for which the latest reading within 3 months was recorded).

### The Mini-Mental State Examination (MMS) \(^{(6)}\)

The MMS measures global cognitive capacity, with component for orientation, attention, short term and immediate recall, and language. With a scores summation of \(> 24\) (out of 30), (See appendix I).

#### Trail making Test B (Trails B) \(^{(7)}\)

This score surveys visuospatial filtering, executive function and concentration (tasks that need working memory and self-moving) by estimating the time required to associate a progression of successive numbered and lettered circles. Shorter consummation times, with a maximum of 300 seconds, show better performance.

### Cognitive decline \(^{(8)}\)

Steady with earlier studies, global cognitive disability was characterized to be a MMs score of fewer than 24, and disabled executive function to be a Trails B score of over 300 seconds.

### Study size calculation:

It was calculated based on methods described previously by Kurella et al. \(^{(5)}\), in which a 5 points difference between CKD and HD in MMs score were chosen, with standard deviation (SD) for CKD group was 8.9 and SD for HD was 12.4, using the MedCalc program \(^{(9)}\). Type I error was 10% and type II error was 80% (detection power). The sample was 59 CKD and 59 HD \(^{(10)}\).

### Vitamin D assessment

Vitamin D \([25\text{(OH)}D]\) levels assessed from each participant, using a direct enzyme immunoassay method \(^{(11)}\). 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

Fifty-six patients with CKD and 61 patients with ESRD on dialysis enrolled in this study, for assessment of baseline there was no significant difference in age, gender, history of hypertension, and coronary artery disease (CAD). History of diabetes, and serum creatinine was significantly 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKD</th>
<th>Dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>56</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Age (y), mean ± SD</td>
<td>52.0 ± 8.8</td>
<td>53.8 ± 9.0</td>
<td>0.489</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (41.1%)</td>
<td>25 (40.9%)</td>
<td>0.766</td>
</tr>
<tr>
<td>Male</td>
<td>33 (58.9%)</td>
<td>36 (59.1%)</td>
<td></td>
</tr>
<tr>
<td>Diabetic, n (%)</td>
<td>20 (35.7%)</td>
<td>32 (52.4%)</td>
<td>0.020</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>51 (91.0%)</td>
<td>49 (80.3%)</td>
<td>0.410</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>22 (39.2%)</td>
<td>25 (40.9%)</td>
<td>0.789</td>
</tr>
</tbody>
</table>
For dialysis patients, 39.3% had deficient 25 (OH) D levels, 34.4% insufficient, 24.5% had sufficient 25 (OH) D levels. Serum 25 (OH) vitamin D was significantly lower in patients on dialysis compared to those with CKD, as illustrated in table (2), and figures (1-2).

### Table (2): assessment of vitamin D

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKD</th>
<th>Dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>56</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>25 (OH)D (ng/mL), mean ± SD</td>
<td>22.1 ± 5.1</td>
<td>15.8 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;12 ng/mL</td>
<td>0 (0%)</td>
<td>24 (39.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 – &lt;20 ng/mL</td>
<td>18 (32.1%)</td>
<td>21 (34.4%)</td>
<td></td>
</tr>
<tr>
<td>≥20 ng/mL</td>
<td>29 (51.7%)</td>
<td>15 (24.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure (1): Number of patients in both CKD and dialysis

Figure (2): Assessment of serum vitamin D levels

Mean MMs score was significantly lower in dialysis patients compared to CKD, while Trail B was significantly higher in dialysis patients, as illustrated in table (3) and figures (3-4).

### Table (3): The Results on Performance Tests and Questionnaire for Subjects with Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD).

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKD</th>
<th>Dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>56</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>MMs</td>
<td>84.5 ± 2.8</td>
<td>75.8 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trails B</td>
<td>146.5 ± 18.6</td>
<td>188.7 ± 33.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

For the Mini-Mental State Examination (MMs), higher scores indicate better performance. For Trails B, lower scores indicate better performance.
**Discussion**

In the present study, mean age of patients was 53.8 ± 9.0 years for patients on dialysis and 52.0 ± 8.8 years for those with CKD, that similar or younger to other studies like, Shaffi et al. (a study in the US involved 255 hemodialysis patients) with age 62.9 ± 16.9 years (12), Jovanovich et al (a study carried out in the USA involved 247 CKD patients, 358 ESRD patients on dialysis) mean age was 69 ± 12 years for CKD patients and 66 ± 11 years for ESRD patients (13), in Kurella et al. study (study carried out in the US involved 80 CKD patients, 80 ESRD patients) mean age for CKD was 64.2 ± 14.2 years, 61.2 ± 14.3 years for ESRD patients (5), 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 (14). In the present study cognitive score was significantly different, it revealed that more cognitive impairment among dialyzed patients compared to patient with CKD without dialysis, these findings were in agreement with other studies like Kurella et al in which they used MMs, Trials B, CVLT immediate recall, CVLT long-delay recall, and found these score had lower cognitive value in ESRD (dialysis) patients compared to CKD (5). In the present study, there was a direct significant correlation between serum creatinine with Trails B score and an inverse correlation with MMs score. The present study there was direct significant correlation between 25 (OH) D with MMs score (r = 0.904, p-value < 0.001) and inverse correlation with Trails B score (r = -0.890, p-value < 0.001), indicating lower vitamin D status correlates with poor cognitive function in patients on dialysis, this is in agreement with other studies like a meta-study by Balion et al. demonstrated level of serum 25(OH)D that of <20 ng/ml is related with decreased cognitive domain (15). Another planned meta-analysis for Italian 858 old people (>65 years) demonstrated an expanded comparative hazard of cognitive impairment for patient with pattern 25(OH)D levels <10 ng/mL, in comparison by people showed levels ≥30 ng/mL finished a 6-year time span (16). Analysis of patients were comparatively youth should to have had a lesser inborn hazard for low level of vitamin D related cognitive impacts, as earlier investigations demonstrated that old patients are fundamentally more vulnerable to CI associated with Hypovitaminosis D (17, 18, 19). Nevertheless, in comparison to hemodialysis patients, peritoneal dialysis patients will additional confined where play out home dialysis. Less social relations will affect their global cognitive capacity as well as outside exposure for sun light could present risk for low vitamin D. In spite of the different contrasts, the general consequences recommend vitamin D lack lead to independent hazard for CI (12, 14).

**Conclusions**

The prevalence of 25(OH) D is high in CKD patients especially those on hemodialysis patients’ deficiency in vitamin D may be related to functions of poor cognitive.

**References**

Abdulzahra & Al Saedi (2020): Effect of low vitamin D in CKD  August 2020  Vol. 23 Issue 12
