Cognitive capacity in individuals with chronic kidney disease: relation to demographic and clinical characteristics

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Submitted on: 05/02/2013.
Approved on: 09/10/2013.

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CAPES.

DOI: 10.5935/0101-2800.20140026

ABSTRACT

Introduction: The life expectancy of individuals with Chronic Kidney Disease (CKD) on hemodialysis has increased, however, with over years in treatment, there is impairment of cognitive function that affect adherence to therapy and dialysis. **Objective:** To evaluate the cognitive ability of individuals on hemodialysis through the Mini Mental State Examination (MMSE) and the relation to sociodemographic and clinical characteristics of these individuals. **Methods:** We obtained demographic and clinical information of 75 individuals. To assess memory and cognition MMSE was applied, which was analyzed according to the different cutoff points proposed in the literature. After classifying the participants according to proposal of different studies, the causes of CKD and sociodemographic characteristics, individuals were divided into groups with and without cognitive impairment in an attempt to identify differences between them. **Results:** Most participants were men with a mean age of 59.2 years. The mean MMSE score was 24.16 points and there was no difference ($p < 0.05$) in MMSE results between the different causes of CKD. MMSE scores were correlated ($p < 0.05$) positively with years of schooling and income and inversely with age. According to the different cutoff points, six to 34 participants showed cognitive impairment and memory, and only three of these were classified with cognitive impairment for all cutoff points evaluated. **Conclusion:** The average MMSE score declined with increasing age and increased with years of schooling and income *per capita*. No relationships were found to justify the harmful effects of dialysis process on cognition and memory.

Keywords: cognition; dialysis; kidney failure, chronic; quality of life.

INTRODUCTION

The recent advances in renal replacement therapies have increased the life expectancy of chronic kidney disease (CKD) patients on hemodialysis.[1] However, as they accumulate years in treatment, cognitive function impairment sets in[2] to considerably affect quality of life, compliance to therapies and dialysis.[3]

Individuals with advanced-stage kidney disease have twice the prevalence of cognitive impairment and dementia of the general population.[2] The first meta-analysis to look into this association found that individuals with CKD are at 65% greater risk of presenting cognitive decline than healthy subjects.[4] Furthermore, cognition impairment in individuals with renal disease is more pronounced in patients on chronic hemodialysis (HD).[5,6] A study comparing changes in the cognitive skills of individuals on HD and seniors (aged 65 years and above) revealed greater decreases in cognition in the group of patients on hemodialysis when compared to elderly individuals.[7]

The causes for such decline are unclear. Compromised protein intake,[2] lower glomerular filtration rate,[3,8,9] particularly when the GFR is under 45 ml/min/1.73 m^2,[3] presence of cardiovascular disease,[5,10] atherosclerotic complications,[11] albuminuria,[9] and anemia[4] have been correlated with cognitive impairment in CKD. Additionally, individuals with CKD usually have multiple comorbidities

and are on multiple drugs, whose side effects and interactions may affect the nervous system.[4] The association between CKD and cognitive impairment has been established, but many are the confounding elements. For example, cardiovascular risk factors, often present in patients with renal disease, have also been correlated with cognitive decline,[10] thus making it harder to assess the possible negative effects of CKD on cognitive function.

The mini-mental state examination (MMSE) developed by Folstein *et al.*[12] and adapted to the Brazilian population[13-15] is a screening tool used to monitor cognitive status recommended by the Ministry of Health, the Brazilian Academy of Neurology, and other international organizations. The MMSE has been frequently used in the evaluation of memory and cognition of CKD patients.[2,3,6,9,16]

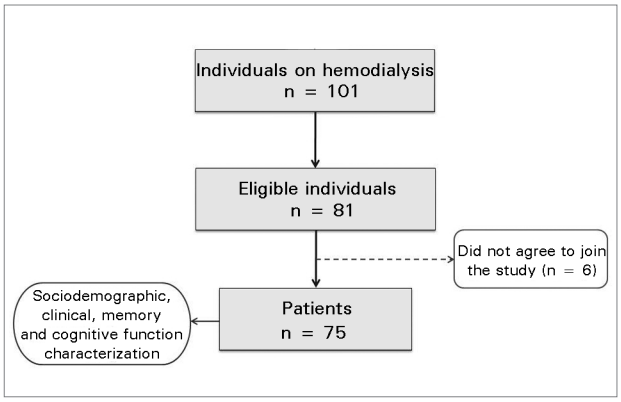
Cognition assessment in individuals with CKD is of the utmost importance. Due to the complexity of this condition, patients are required to process and understand significant amounts of information in order to properly comply with the treatment. Early diagnosis and intervention help contain or mitigate the progress of cognitive impairment.[4,5] This study aimed to assess the cognitive skills of individuals with CKD on chronic hemodialysis through the MMSE and examine the possible correlations between cognitive status and patient sociodemographic and clinical characteristics.

Methods

This observational analytical study was carried out in a nephrology service in Viçosa, Minas Gerais, Brazil.

The study enrolled individuals aged 18 or older on hemodialysis for at least three months. Enrolled subjects were required to give informed consent. Individuals diagnosed with hearing loss, visual impairment, or acute kidney injury, with recently implanted catheters, positive for hepatitis B or C viruses, and on glucocorticoids were not included in the study. Eighty-one of the 101 subjects on HD met the enrollment criteria and were invited to join the study, and 75 gave written consent (Figure 1).

Figure 1. Patient selection representation.



The data used in this study were obtained from the patient charts maintained in the nephrology service and from the MMSE. Personal data related to renal disease such as underlying conditions, date of the first HD session, and type of HD access were gathered from patient charts. Laboratory test results and prescriptions were also obtained from patient charts and included number of prescribed medications, Kt/V, serum albumin, pre and post-dialysis urea, creatinine, calcium, phosphorus, and parathyroid hormone (PTH). The calcium-phosphorus product (mg^2/dL^2) was analyzed for the ratio between both minerals. As set in the recommendations of the Brazilian Clinical Practice Guidelines for Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD),[17] albumin-corrected calcium serum levels were used as per the following formula: corrected calcium = total serum calcium + [(4-serum albumin) x 0.8].

The MMSE was used to assess patient memory and cognition. Patients were interviewed during home visits or during the course of the second HD session of the week (starting at least 30 minutes after the start of the session and ending no later than 30 minutes before the end of the session) if their arteriovenous fistulas, catheters, and other conditions allowed them to write and draw. Cognitive function was categorized based on the the cutoff points indicated by Folstein *et al.*[12] - score of 24 or lower - and Murden *et al.*,[18] Bertolucci *et al.*,[13] Almeida,[14] Brucki *et al.*[15] and Lourenço & Veras[19] for the general population, in which scores are differentiated based on level of education

(Chart 1). The ratings obtained by the different cutoff points were compared, as were the groups of individuals with and without involvement based on the approaches proposed by different authors to analyze possible differences between groups.

One of the authors treated the data sets. The findings were presented in tables and described in the form of mean values and standard deviations (SD), median values, and minimum and maximum values. The Kolmogorov-Smirnov test was used to test the normality of the distribution, indicating the use of parametric or non-parametric tests for analysis.

The difference between continuous variables was assessed using *Student's t*-test and the Mann-Whitney U test, when appropriate, in addition to ANOVA and Multiple Comparisons. Associations between clinical and demographic variables and MMSE scores were assessed using the Pearson or Spearman correlations, according to the distribution of the variables. A confidence level of 95% was adopted to reject the null hypothesis. All statistical analyses were performed using SPSS for Windows (version 20.0).

The protocol of this study was submitted to and approved by the Internship Committee of the hospital and by the Ethics Committee on Human Research (CEPH) of the Federal University of Viçosa (Nº 002/2012/CEPH).

Results

Seventy-five patients were enrolled in this study. Most were males (60 %, n = 45) and Caucasians (57.4%, n = 41). Patient mean age was 59.2 years (SD = 13.44) and 37 individuals (49.3%) were aged 41-59 years. The main causes of CKD in the studied population were *diabetes mellitus* (33.3%, n = 25) and hypertension (32%, n = 24). Patients had been on dialysis for three to 220 months and for a mean of 62.88 months (SD = 53.08), and most individuals had been on HD for less than 60 months (57.3%, n = 43). Arteriovenous fistulas (AVF) were the most common type of venous access, and were used by 68 (90.7 %) subjects on hemodialysis. The mean Kt/V was 1.69 (SD = 0.34).

The MMSE yielded a mean score of 24.16 (SD = 4.49) in cognitive function assessment, with scores ranging from seven to thirty. The lowest scores were seen in the domain assessing patient attention and calculation skills, with a score of two out of five points. There was no difference in the MMSE scores between the different causes of CKD ($p = 0.140$).

The correlations between MMSE scores and sociodemographic, clinical and biochemical variables were tested (Table 1). MMSE scores correlated ($p < 0.05$) only with demographic data, showing direct associations with years of schooling and *per capita* income, and an inverse correlation with age. Significant differences in MMSE scores were seen between genders ($p = 0.008$) and age ranges ($p = 0.018$); males and individuals aged 60 years and younger had higher scores on the MMSE. No differences were found between genders in terms of schooling ($p = 0.144$) and *per capita* income ($p = 1.000$), and individuals aged 60 and younger did not differ from individuals over 60 years of age in terms of schooling ($p = 0.165$) or *per capita* income ($p = 0.206$), indicating the significance of gender and age on MMSE scores regardless of years of education and *per capita* income.

Chart 1 Different cutoff points for the categorization of cognitive function using the mini-mental state examination according to level of education

Cutoff points*	Number of year in school							
	0	0-3	> 1	1-4	> 4	5-8	9-11	> 11
Bertolucci *et al.*[13]	13	-	-	18	26	-	-	-
Almeida[14]	20	-	24	-	-	-	-	-
Brucki *et al.*[15]	20	-	-	25	-	26.5	28	29
Murden *et al.*[18]	17	-	-	24	-	-	-	-
Lourenço & Veras[19]	19	-	25	-	-	-	-	-

* Values lower than cutoff points indicate cognitive involvement.

Table 1 Single correlations between mini-mental state examination (MMSE) scores and time on dialysis and sociodemographic and biochemical variables of individuals on hemodialysis - Viçosa, MG - 2013

	MMSE	
Variables	R	*p*
Time on dialysos (months)	-0.136[a]	0.243
Age (years)	-0.333[a]	0.003**
Years of schooling	0.752[b]	0.000**
Per capita income	0.287[b]	0.013**
Comorbidities	0.036[a]	0.764
Albumin (g/dL)	0.014[a]	0.904
Creatinine (mg/dL)	0.142[a]	0.223
Pre-dialysis urea (mg/dL)	0.158[a]	0.176
Post-dialysis urea (mg/dL)	0.190[a]	0.103
Calcium (mg/dL)	0.61[a]	0.602
Corrected calcium[#] (mg/dL)	0.057[a]	0.625
Phosphorus (mg/dL)	0.062[a]	0.596
Calcium-phosphorus product (mg^2/dL^2)	0.080[a]	0.496
Corrected calcium[#] phosphorus product (mg^2/dL^2)	0.080[a]	0.496
PTH[##] (pg/dL)	-0.003[b]	0.980
Kt/V	-0.065[a]	0.579

[#] Serum albumin-corrected calcium, as per the formula: corrected calcium = total serum calcium + [(4-serum albumin) x 0.8]; [##] PTH: parathyroid hormone; [a] Pearson's correlation coefficient; [b] Spearman's rank correlation coefficient; * $p < 0.05$; ** $p < 0.01$.

MMSE scores were analyzed along with level of education based on the cutoff points proposed by several authors,[12-15,18,19] and six different categorizations of cognitive and memory impairment were obtained for 34 patients (Table 2). Only three individuals were categorized as having cognitive and memory impairment for all proposed cutoff points; these subjects had been to school for zero, two and eleven years and attained scores of seven, 16, and 23, respectively.

MMSE scores were used to divide patients into groups with and without cognitive and memory impairment. No statistically significant differences ($p < 0.05$) were found for sociodemographic and biochemical variables based on the categorization proposed by Murden *et al.*,[18] Bertolucci *et al.*[13] and Brucki *et al.*[15] However, according to the classification published by Almeida,[14] patients with higher levels of education ($p = 0.036$) and *per capita* income ($p = 0.016$) had no cognitive or memory impairment. According to Lourenço & Veras,[19] individuals without cognitive impairment had higher levels of *per capita* income ($p = 0.027$) than their counterparts with cognitive impairment. According to Folstein *et al.*,[12] better educated individuals ($p = 0.000$), subjects with higher levels of *per capita* income ($p = 0.007$), and patients with higher levels of serum calcium, both corrected ($p = 0.046$) and uncorrected ($p = 0.039$) for albumin, had no cognitive or memory impairment.

Discussion

The cognitive skills of 75 individuals on chronic HD were assessed to elicit possible correlations between cognition and clinical and sociodemographic variables. The studied population presented characteristics commonly seen in local and international studies comprising individuals on HD: most were males[3,6,20-24] and Caucasians.[24,25] As in the present study, Sehgal *et al.*[2] and Frankenfield *et al.*[20] reported diabetes, followed by hypertension, accounted for most cases of CKD, indicating that diabetes may be the main cause of kidney failure not only in developed nations,[25] but also in developing countries, as indicated by this study. The projected increase in the prevalence of hypertension, diabetes, and obesity,[26] the latter a risk factor for the first two, suggests a rise in the number of cases of CKD.

Table 2 Categorization of individuals on hemodialysis for cognition and memory according to cutoff points proposed by various authors - Viçosa, MG - 2013

Authors	Cognitive and memory impairment	
	Yes	No
Folstein *et al.*[12]	34	41
Murden *et al.*[18]	8	67
Bertolucci *et al.*[13]	6	69
Almeida[14]	15	60
Brucki *et al.*[15]	25	50
Lourenço & Veras[19]	22	53

Cutoff points (number of years of schooling: MMSE score):[13] - ≤ 24;[19] - 0 to 3 years: 17; > 4 years: 24;[14] - 0 years: 13; 1 to 4 years: 18; > 5 years: 26;[15] - 0 years: 20; > 1 year: 24;[16] - 0 years: 20; 1 to 4 years: 25; 5 to 8 years: 26.5; 9 to 11 years: 28; > 11 years: 29;[20] - 0 years: 19; > 1 year: 25.

The mean time of 62.88 months on dialysis seen in the studied population was similar to the mean time found in other Brazilian studies with hemodialysis patients.[6,23] Many of the individuals were adults with a mean age was close to that reported by Condé *et al*.[6] for dialysis patients seen in Juiz de Fora, MG, Brazil, and higher than the mean age reported in studies carried out in the United States.[21,24] The high prevalence of AVF in hemodialysis patients may represent savings to the health care system as fistulas can be left in place for a long time, in addition to benefitting individuals with CKD, as AVFs have been correlated with lower incidence of complications and infection.[27]

Studies have shown that individuals on hemodialysis had lower cognition and memory scores than the general population.[3,6,7] According to Murray *et al.*,[28] patients on hemodialysis are 3.54 times more likely to have cognitive impairment than healthy individuals of the same age. The mean score of the studied population was similar to the median score of healthy individuals with lower levels of education,[13,15] higher than the scores observed in a group of seniors on HD[7] and elderly subjects without CKD with at least one year of schooling,[29] but lower than the mean score obtained for a sample of healthy Brazilian individuals,[30] pointing to disagreements on the negative effects of hemodialysis on cognition and memory.

The impact of level of education and age seen in this study, previously established for healthy populations,[13,15,30] has also been confirmed for subjects on HD.[2,7] However, when patients were divided into groups of individuals with and without cognitive impairment according to the many cutoff points published in the literature, only level of education and household income were verified to have been higher among individuals without cognitive impairment. Even the categorization proposed by Folstein *et al.*,[12] in which cutoff points are not stratified by level of education, individuals categorized as cognitively impaired had fewer years of formal education.

There is no consensus in the literature over the protective effect of higher levels of education against lower scores in cognitive skill tests.[6] Literacy may be a more decisive factor than the level of education not only within the realm of cognitive function, as it also impacts one's ability to understand commands and take appropriate action to comply with the proposed course of therapy.[31] However, there currently are no instruments capable of measuring literacy, particularly in health care.

Considering gender differences, other authors have also reported higher scores among male subjects.[7,15] A study with healthy individuals revealed that women with fewer years of education had lower MMSE scores than men with low and high levels of education.[30] No differences between genders were found in this study when levels of income and education were considered, suggesting that the diversity in results may be due to more specific distinctions between genders, or social (more stimuli) and biological factors.

In this study, elderly patients had lower MMSE scores, although without differences in terms of levels of income and education. Decline in physical

and cognitive skills, with diminished information processing rates, are natural consequences of aging.[6] Hemodialysis and the intense catabolism characteristically seen in CKD may contribute to and maximize the aging of the brain. When compared to other individuals, patients on HD with lower[6] or equal[7,8] mean ages in relation to their counterparts had lower scores on cognitive skill tests. Bossola *et al*.[32] reported older individuals on HD had lower scores in the MMSE and correlated this finding with the greater number of comorbidities and symptoms of depression they presented. The correlation between symptoms of depression and lower cognitive test scores has been described.[7] Interestingly, depression and dementia or cognitive impairment are commonly observed in patients with CKD and may be correlated to each other, although further clarification is still needed. Birmelé *et al*.[33] studied a population of 300 individuals on HD and correlated greater numbers of signs of depression and comorbidities with lower mental test scores. In this population, the authors found 10.3% of individuals had dementia. Feroze *et al*.[34] assessed 170 individuals on dialysis and reported 36% of them had some degree of depression, and 21% had moderate to severe depression.

Our study failed to establish correlations between MMSE scores and biochemical variables albumin - as similarly reported by Hailpern *et al*.,[8] creatinine - as described by Hailpern *et al*.,[8] Condé *et al*.[6] and Bossola *et al*.,[7] urea - as reported by Condé *et al*.[6] and Bossola *et al*.,[7] calcium and phosphorus - in agreement with Condé *et al*.,[6] and PTH - as also observed by Bossola *et al*.[7] No correlations were found in this study between MMSE scores, number of comorbidities, and time on HD, as also reported by Sehgal *et al*.,[2] Griva *et al*.[35] and Bossola *et al*.[7] However, other authors have described correlations between cognitive involvement and poor protein nutritional status,[2] higher creatinine levels,[3] lower levels of serum hemoglobin[6] and albumin.[35]

Improvements in the effectiveness of dialysis[1] may have reduced the potential impact of HD on patient cognitive function. Kurella Tamura *et al*.[36] looked into the impact of hemodialysis upon the cognitive function of chronic renal patients and found no differences between individuals enrolled in programs with three or six HD sessions per week, suggesting residual syndrome is not the cause of the cognitive impairment seen in patients on HD. The biochemical parameters analyzed in the studied population were not much above or below desired levels (data not shown), suggesting patients complied with the proposed therapy and effectively managed CKD and the existing comorbidities, thus mitigating possible impacts on test results.

In the categorization proposed by Folstein *et al*.,[12] individuals without cognitive and memory impairment had unexpectedly higher serum calcium levels, albumin-corrected or not. The association between high levels of serum phosphorus and calcium may produce extraosseous calcification and increase the patient's risk for cardiovascular events.[37] Cardiovascular diseases rank atop the causes of cognitive impairment in the general population.[38] The high levels of calcium found in cognitively impaired individuals with or without CKD may be correlated with blood vessel calcifications, reduced cerebral blood flow and impaired neuronal synapses.[3] Beck *et al*.[39] analyzed two cases of hyperphosphatemic tumoral calcinosis with dementia and suggested a correlation between cognitive impairment and abnormal deposition of calcium and phosphorus in the arteries.

In this study, serum calcium values corrected and uncorrected for albumin ranged from 7.44 to 11.4 mg/dL and 7.2 to 10.8 mg/dL, respectively, showing the higher values found in the studied individuals do not refer to hypercalcemia, but to levels within the desired range between 9 and 11 mg/dL,[17] known to be favorable to mental health when compared to hypocalcemia.

Conclusions

Mean MMSE scores decreased with increases in patient age and were higher among patients with higher levels of education and income. Six of 34 patients had cognitive and memory impairment in all different scales used in the assessment. However, no correlations were found to explain the harmful effects of hemodialysis on cognition and memory.

Nonetheless, the importance of assessing cognitive and memory skills of individuals with chronic kidney disease cannot be denied,

given the complex nature of this condition and the need for patients to understand medical recommendations in order to appropriately comply with the prescribed treatment. As a tool to assess cognition and memory, the MMSE can be easily used for patient screening purposes and monitoring of individuals in all stages of CKD.

However, more studies with representative populations of CKD patients at different stages of the disease are needed to define suitable cutoff points that take the characteristics of these individuals into account.

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