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Correlation between Cognitive Dysfunction and Serum Magnesium, Calcium and Phosphorus Level in the Elderly Egyptian Patients in Zagazig University Hospitals

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ABSTRACT

Background: Many elderly neurological disorders are associated with phosphate, magnesium, and calcium deficiency. **Objective:** To assess the correlation between cognitive dysfunction and serum magnesium, calcium and phosphorus level in the elderly Egyptian patients. **Patients and Methods:** From July 2021 to October 2021, at Zagazig University Hospitals inpatient and outpatient clinics of Internal Medicine Department, our case control trial was conducted on 94 elderly patients with and without impaired cognitive function, they were divided into two equal groups (47 each group). All patients underwent a laboratory investigation to assess serum levels of magnesium, calcium, and phosphorus. Assessment of cognitive function was done through answering a series of questions and/or performing simple tasks. **Results:** There was highly statistically significant correlation between the two studied groups (normal and abnormal cognitive functions) and serum calcium, magnesium, and phosphorus levels ($P < 0.001$ for the 3 correlations), there was statistically significant correlation between Mg^{2+} and Montreal Cognitive Assessment (MoCA) test, Mini mental state examination and Recall Mini-COG test in abnormal group, there was statistically significant correlation between P^{3+} and age in abnormal cognitive functions group, MoCA test, Mini mental state examination and Recall Mini-COG test in abnormal group. **Conclusion**: Calcium and magnesium are associated with cognitive improvement in elderly, but in contrast, higher level of phosphorus facilitates cognitive decline. We concluded that age, magnesium and phosphorus were independent variable for cognitive impairment.

Keywords: Calcium, Cognitive Dysfunction, Magnesium, Phosphorus.

INTRODUCTION

Elderly individuals with cognitive abnormalities face a range of challenges, including decreased quality of life, repeated hospitalization, and a requirement for in-home nursing care [(1)]**.** Many age-related central nervous system (CNS) disorders can be traced back to nutritional deficiencies. Neurocognitive capabilities in the elderly are influenced by a number of factors, including nutrition**.** Magnesium, calcium, and phosphorus-rich foods, nuts, and seafood are quite beneficial. Due to a decrease in the amount of vegetables consumed, the levels of these macronutrients in the serum have decreased [(2)]**.**

Many enzymatic functions rely on magnesium, which is one of the most abundant cations in the bodily fluid. A lack of magnesium in one's diet increases the risk of neuronal toxicity. Magnesium is required for appropriate CNS function. Numerous essential processes, including as tone modulation, RNA, DNA, protein synthesis, membrane integrity and fluidity rely on magnesium. Magnesium's bioenergetic and metabolic activities are critical to brain function [(3)]**.**

Low levels of serum magnesium, a nutritional status marker, increase the risk of cardiovascular disease and diabetes mellitus, both of which are associated with cognitive decline [(2)]**.** Increased stool and urine loss, decreased nutrition and the inability of the intestines to absorb magnesium are all factors that contribute to magnesium shortage in the elderly. Osteoporosis in older women can cause magnesium metabolism to be disrupted between bone and blood [(4)]**.**

Many elderly neurological disorders are caused in part by low levels of calcium, magnesium, as well as phosphorus [(5)]**.** Phosphorus is widely available in human brains and is necessary for a wide range of physiological functions, including energy storage, bone and muscle development, hormone balancing, and the metabolism of brain cells**.** Phosphorus levels in patients with chronic kidney disease are disrupted, which leads to dementia**.** Increased serum phosphorus levels were found to be associated with a significant increase in the risk of cognitive impairment in a cross-sectional investigation of 422 chronic renal disease patients who lived in the community [(6)]**.**

The aim of the present study was to assess the correlation between cognitive dysfunction and serum magnesium, calcium and phosphorus level in the elderly Egyptian patients.

PATIENTS AND METHODS

From July 2021 to October 2021, at Zagazig University Hospitals inpatient and outpatient clinics of Internal Medicine Department, our case control trial was conducted on 94 elderly patients with and without impaired cognitive function, they were divided into two equal groups (47 each group): Group 1: Patients with symptoms, signs of impaired cognitive function, and Group 2: healthy elderly with no symptoms, signs of impaired cognitive function. Zagazig University's Biochemistry Department handled the technical aspects.

Ethical considerations:

When all participants completed informed permission papers and submitted them to the research ethics committee at Zagazig University, the study was permitted (ZU-IRB#6965). Ethics guidelines for human experimentation were adhered to in line with the Helsinki Declaration of the World Medical Association.

Inclusion Criteria: Age: ≥ 65 years, sex: both sex female and male,

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Exclusion Criteria: Stroke, head trauma, neurological disease, mental illness or any other known present condition with reduced cognitive function or on drugs that induce impaired cognition, already patients with impaired cognition, drugs that alter serum electrolytes, particularly magnesium, calcium, and phosphorus, which can impair cognitive performance in patients, and in this study, patients who had a history of cancer or radiation therapy, as well as those who had active infections such as bone and muscle illness, cardiac, parathyroid, chronic renal disease, and nephrotic syndrome, were not eligible.

All participants of the study were subjected to:

A) Full history and thorough clinical examination

B) Laboratory investigations:

Routine laboratory investigations were performed according to Clinical Pathology Department Protocol in Zagazig University Hospitals: **Complete blood picture (CBC), liver function tests including serum albumin, kidney function tests (serum creatinine, serum urea), INR, and serum calcium (mg/dl), serum phosphorus (mg/dl) and serum magnesium (mg/dl).**

Assessment of cognitive function using MoCA: MoCA comprises 30 items separated into the domains of attention, language, memory, visuospatial, executive processes, and orientation and scored appropriately from 0 to 30 with a cutoff of 26. A normal score was one with a minimum of 26 points. **(Figure 1)** [7].

Assessment of cognitive function using Mini-Mental State Examination (MMSE) (Figure 2) [8].

Assessment of cognitive function using Mini-Cog: Using a delayed recall item and a clock-drawing exam, the Mini-Cog is a cognitive screening instrument. The Mini-Cog can be administered in less than three minutes and was designed and tested on older adults living in the community **(Figure 3)** [8].

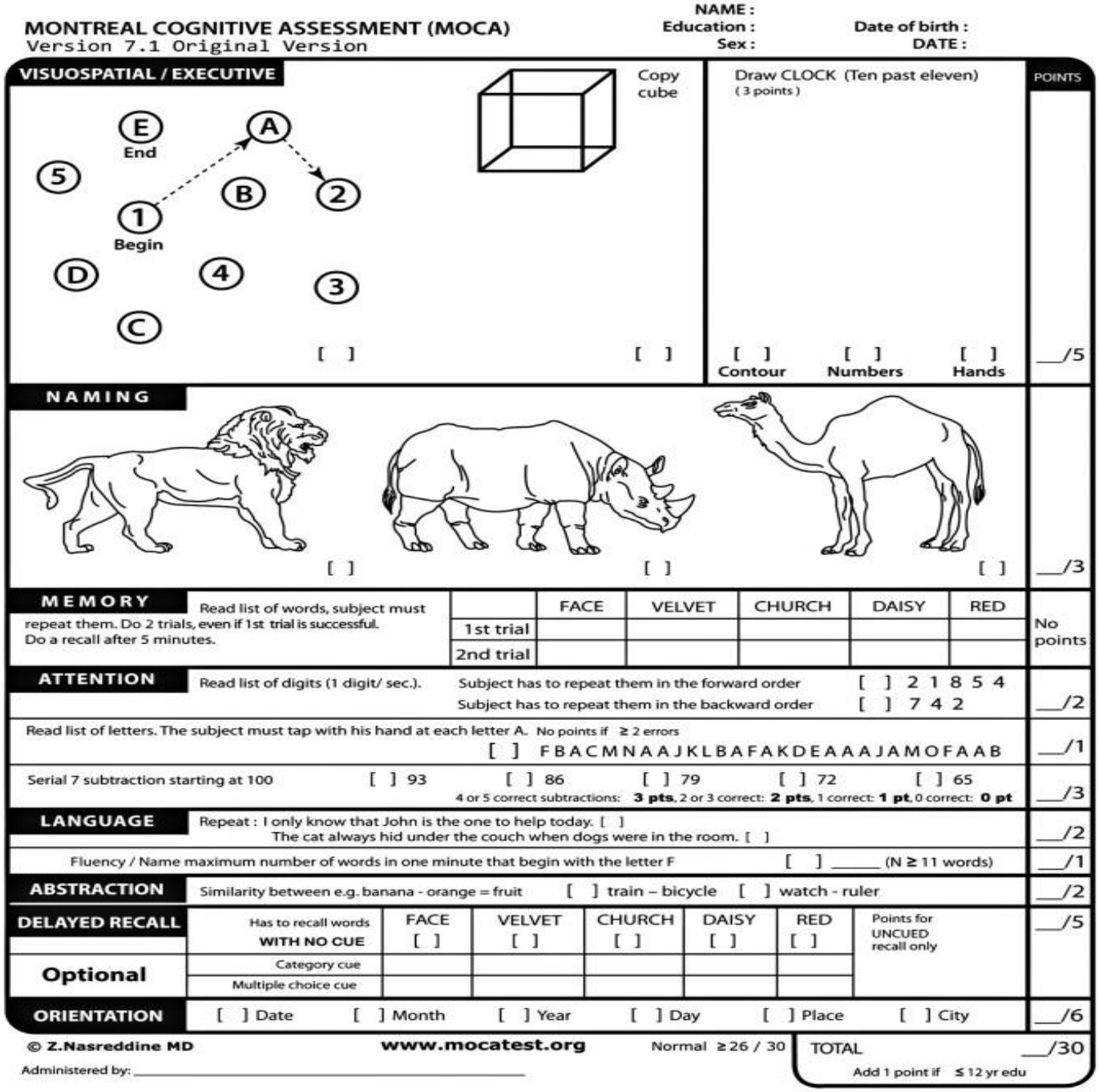
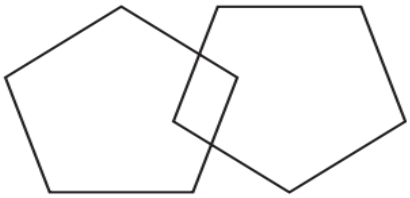


Figure (1): Montreal Cognitive Assessment (MoCA) test[7]

Assessment of cognitive function using MMSE:

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

Figure (2): Mini-Mental State Examination (MMSE) Test[8].

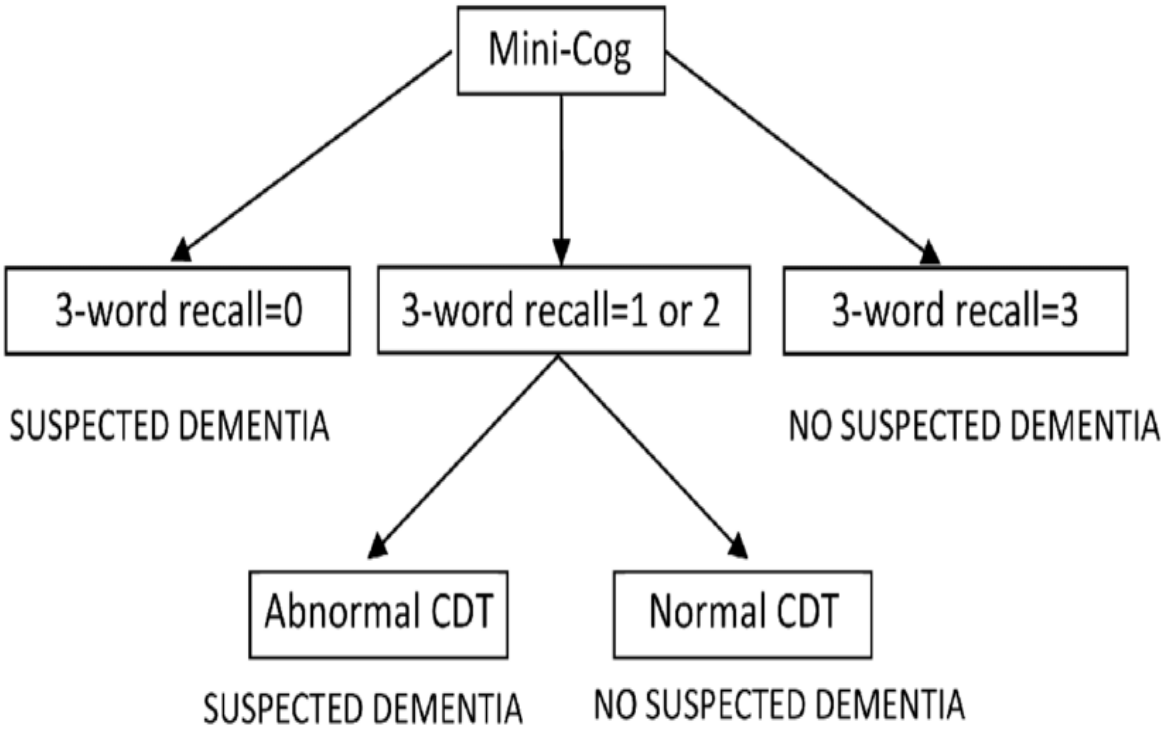


Figure (3): Mini-Cog Test[8]

Statistical analysis

Using SPSS software (USA) version 16. Numbers and percentages were used to represent qualitative data, which were compared by the Chi square (X^2) test, Fisher's Exact or Monte Carlo correction. Mean ± SD, median, and interquartile range (IQR) were used to represent quantitative data, which were compared by Student t-test or Mann Whitney test. $P \leq 0.05$ was considered statistically significant and $P \leq 0.001$ was considered highly significant.

RESULTS

(Table 1) shows that a significant difference was existed between the two groups (those with normal and deficient cognitive functions), as regard education and age.

Table (1): Comparison between the two studied groups according to demographic data

Demographic data	Cognitive functions				Test of Sig.	P
	Normal (n = 47)		Abnormal (n = 47)			
	No.	%	No.	%		
Sex						
Male	25	53.2	27	57.4	χ^2= 0.172	0.678
Female	22	46.8	20	42.6		
Education						
<12 years	14	29.8	21	44.7	χ^2= 32.114*	<0.001**
12 years	0	0.0	17	36.2		
>12 years	33	70.2	9	19.1		
Age (years)						
Min. – Max.	65.0 – 75.0		65.0 – 78.0		Mann Whitney= 840.50*	0.043*
Mean ± SD.	68.11 ± 2.03		69.38 ± 2.86			
Median (IQR)	68.0 (66.50 – 69.50)		69.0 (67.50 – 70.0)			

*: Statistically significant, **: Statistically highly significant

(Table 2) shows that there was highly statistically significant difference between the two studied groups (normal and abnormal cognitive functions) as regard **Ca^{2+}**, Mg^{2+} and P^{3+}.

Table (2): Serum calcium (Ca^{2+}), magnesium (Mg^{+}), and phosphorus (P^{3+}) levels in the two studied groups

Ca^{2+} (mg/dl)	Cognitive functions		T	P
	Normal	Abnormal		
Male	**(n = 25)**	**(n = 27)**		
Min. – Max.	9.0 – 10.20	8.02 – 8.90		
Mean ± SD.	9.62 ± 0.38	8.44 ± 0.22	13.430	<0.001**
Median (IQR)	9.60 (9.29 – 9.96)	8.42 (8.28 – 8.59)		
Female	**(n = 22)**	**(n = 20)**		
Min. – Max.	8.98 – 10.20	7.99 – 8.47		
Mean ± SD.	9.52 ± 0.36	8.17 ± 0.15	16.355	<0.001**
Median (IQR)	9.58 (9.19 – 9.72)	8.19 (8.02 – 8.30)		

Mg^{2+} (mg/dl)	Cognitive functions		T	P
	Normal (n = 47)	Abnormal (n = 47)		
Mean ± SD.	2.11 ± 0.15	1.54 ± 0.20	16.011	<0.001**

(P^{3+} mg/dl)	Cognitive functions		T	p
	Normal (n = 47)	Abnormal (n = 47)		
Mean ± SD.	3.55 ± 0.48	4.24 ± 0.71	5.488	<0.001**

**: Statistically highly significant

(Table 3) shows that there was statistically insignificant correlation between Ca^{2+} and different parameters in each group (normal and abnormal cognitive functions groups).

Table (3): Correlation between Ca^{2+} and different parameters in each group

Ca^{2+} (mg/dl) vs.	Cognitive functions			
	Normal (n = 47)		Abnormal (n = 47)	
	r	p	r	p
Age (years)	0.070	0.641	-0.244	0.099
MoCA test				
Visuspatial/ executive	0.257	0.081	-0.102	0.497
Naming	–	–	-0.108	0.471
Attention	-0.010	0.947	-0.113	0.448
Language	-0.016	0.915	0.127	0.393
Abstraction	-0.074	0.623	0.140	0.348
Delay recall	0.040	0.789	0.119	0.424
Orientation	–	–	0.157	0.292
Score	0.084	0.573	0.056	0.710
Mini mental state examination				
Orientation	–	–	0.036	0.809
Registration	–	–	-0.222	0.133
Attention and calculation	0.097	0.518	-0.025	0.869
Recall	0.096	0.521	0.127	0.395
Language	0.016	0.917	-0.033	0.824
Copying	–	–	0.088	0.557
Score	0.095	0.525	-0.002	0.991
Recall Mini - COG test	0.096	0.521	0.127	0.395

(Table 4) shows that there was statistically significant correlation between Mg^{2+} and MoCA test (Visuspatial/executive, attention, language, and score in abnormal group, and delay recall in both abnormal and normal group), mini mental state examination (Orientation, recall, language and score in abnormal group) and recall mini-COG test in abnormal group.

Table (4): Correlation between 2+Mg and different parameters in each group

Mg^{2+} (mg/dl) vs.	Cognitive functions			
	Normal (n = 47)		Abnormal (n = 47)	
	r	p	r	p
Age (years)	-0.119	0.427	-0.236	0.110
MoCA test				
Visuspatial/executive	-0.071	0.636	0.481	0.001**
Naming	–	–	0.281	0.055
Attention	-0.071	0.637	0.340	0.019*
Language	-0.140	0.349	0.484	0.001**
Abstraction	-0.067	0.656	0.284	0.053
Delay recall	0.069	0.644	0.312	0.032*
Orientation	–	–	0.080	0.594
Score	-0.085	0.571	0.513	<0.001**
Mini mental state examination				
Orientation	–	–	0.476	0.001**
Registration	–	–	0.225	0.128
Attention and calculation	0.023	0.877	0.250	0.090
Recall	0.094	0.531	0.320	0.028*
Language	0.005	0.971	0.327	0.025*
Copying	–	–	0.198	0.182
Score	0.018	0.905	0.582	<0.001**
Recall Mini-COG test	0.094	0.531	0.320	0.028*

*: Statistically significant, **: Statistically highly significant

(Table 5) shows that there was statistically significant correlation between P^{3+} and age in abnormal cognitive functions group, MoCA test (Visuspatial/executive, attention, language, abstraction, delay recall and score in abnormal group), Mini mental state examination (orientation, recall and score in abnormal group) and recall mini-COG test in abnormal group.

Table (5): Correlation between P^{3+} and different parameters in each group

P^{3+} (mg/dl) vs.	Cognitive functions			
	Normal (n = 47)		Abnormal (n = 47)	
	r	p	r	p
Age (years)	0.088	0.555	0.376	0.009*
MOCA test				
Visuspatial/executive	-0.122	0.416	-0.433	0.002*
Naming	–	–	-0.099	0.508
Attention	0.036	0.809	-0.362	0.012*
Language	-0.258	0.080	-0.334	0.022*
Abstraction	0.119	0.424	-0.430	0.003*
Delay recall	0.157	0.291	-0.481	0.001**
Orientation	–	–	-0.143	0.339
Score	0.039	0.797	-0.523	<0.001**
Mini mental state examination				
Orientation	–	–	-0.422	0.003*
Registration	–	–	-0.018	0.906
Attention and calculation	-0.264	0.073	-0.279	0.058
Recall	-0.237	0.109	-0.598	<0.001**
Language	0.148	0.321	-0.218	0.141
Copying	–	–	-0.077	0.606
Score	-0.247	0.094	-0.519	<0.001**
Recall Mini - COG test	-0.237	0.109	-0.598	<0.001**

*: Statistically significant, **: Statistically highly significant

(Table 6) shows that, by using univariate logistic regression analysis, the factors affecting abnormal cognitive functions were age, ALT, AST, Visuspatial/executive MoCA, language MMSE, Mg^{+2} and $P3^{+3}$.

Table (6): Univariate and multivariate logistic regression analysis for the parameters affecting abnormal cognitive functions (n = 47)

	Univariate		Multivariate	
	P	**OR (95%C.I)**	**p**	**OR (95%C.I)**
Gender (Male)	0.678	1.188 (.526 – 2.681)		
Age (years)	0.021*	1.251 (1.035 – 1.512)	0.892	1.073 (0.392-2.936)
Education (>12 years**)**	0.999	-		
WBC ($\times 10^3$)	0.219	1.131 (0.929 – 1.377)		
Hgb (g/dl)	0.922	1.019 (0.694 – 1.496)		
PLT ($\times 10^3$)	0.561	1.001 (0.997 – 1.006)		
Total bilirubin (mg/dl)	0.894	1.108(0.245-5.015)		
Direct bilirubin	0.751	0.725(0.099-5.301)		
ALT (U/L)	0.002*	1.147(1.051-1.252)	0.343	1.607 (0.603-4.283)
AST (U/L)	<0.001**	1.177(1.096-1.265)	0.439	1.183 (0.773-1.811)
Total protein (g/dl)	0.453	0.693(0.266-1.804)		
Albumin (g/dl)	0.838	0.880(0.259-2.996)		
INR	0.496	0.432(0.039-4.845)		
Creatinine (mg/dl)	0.435	0.557(0.128-2.424)		
Visuspatial/ executive MoCA	<0.001**	0.016(0.002-0.122)	0.230	0.001(0.0001-77.258)
Naming MoCA	0.999	-		
Memory MoCA	0.999	-		
Attention MoCA	0.999	-		
Language MoCA	0.997	-		
Abstraction MoCA	0.999	-		
Delay recall MoCA	0.999	-		
Orientation MoCA	0.997	-		
Score MoCA	0.992	-		
Orientation MMSE	0.992	-		
Registration MMSE	0.999	-		
Attention and calculation MMSE	0.996	-		
Recall MMSE	0.997	-		
Language MMSE	<0.001**	0.063(0.022-0.180)	0.185	0.035(0.001-4.970)
Copying MMSE	0.999	-		
Score MMSE	0.987	-		
Recall Mini-COG test	0.997	-		
Ca^{+2} (mg/dl)	0.979	-		
Mg^{+2} (mg/dl)	<0.001**	0.001(.0001-0.001)	0.069	0.001(0.0001-2.671)
P^{3+} (mg/dl)	<0.001**	6.355(2.739-14.741)	0.957	1.097 (0.038-31.99)

*: Statistically significant, **: Statistically highly significant

DISCUSSION

An increasingly pressing concern in public health is the declining cognitive function of the world's ageing population [9]. Mild cognitive impairment can lead to cognitive dysfunction, while severe cognitive impairment can lead to dementia or Alzheimer's disease (AD), making it impossible for the elderly to carry out their everyday activities without assistance. One of the most terrifying elements of ageing is cognitive deterioration [10].

Many researchers have been looking into the connection between certain ions including phosphorus, magnesium, and calcium, which are known to play an important role in the pathogenesis of age-related neurological abnormalities. When compared to healthy controls, the aluminum concentrations in the brains of people with AD were higher, but magnesium and phosphorus concentrations were lower. AD patients also reported lower plasma magnesium, selenium, zinc, copper, as well as iron levels than healthy individuals [5].

In the current study, regarding sex among healthy control group, there were 25 (53.2%) males compared to 22 (46.8%) females, also about 27 (57.4%) males and 20 (42.6%) females were observed to experience cognitive impairment, with non-statistically significant between these groups. These findings were consistent with **Ashraf *et al.*** [11] who quantify the plasma elemental concentrations in sex matched individual among healthy and impaired cognitive patients.

As regard education, there was a high statistical significance among the two studied groups (normal and cognitive dysfunction patients) in terms of education levels, where the higher education levels (who have educated more than 12 years) were associated with normal cognitive function with (n=33, 70.2%) compared to (n=9, 19.1%) with abnormal cognitive function. As regard age, the mean age in normal cognitive patients' group was 68.11 ± 2.03 and ranged between 65 to 75 years and the mean age in abnormal cognitive patients' group was 69.38 ± 2.86 ranged between 65 to 78 years, which was higher than normal control group, with statistical significance difference between the two groups.

Therefore, age and education level were risk factors for cognitive impairment, and our previous findings were consistent with **Bai *et al.*** [12].

In our study there was highly statistically significant difference between the two studied groups (normal and abnormal cognitive functions) and serum calcium level as the mean calcium level in normal cognitive functions group was 9.57 ± 0.37 SD with range (9.20 – 9.94) higher than the mean calcium level in abnormal cognitive functions group 8.33 ± 0.23 SD with range (8.10 – 8.56). This was confirmed by **Zhen *et al.*** [13] who reported that AD patients showed lower serum calcium than control patients in cross-sectional cohort studies. We were not online with **Ma *et al.*** [14] who found that high serum calcium increased the cognitive decline and the conversion from non-demented status (cognitively normal and MCI) to AD.

We conducted that there was statistically significant difference between the two studied groups (normal and abnormal cognitive functions) and magnesium, where the mean magnesium in abnormal cognitive functions group 1.54 ± 0.20 SD with range (1.30 – 2.30) was lower than the mean magnesium in normal cognitive functions group 2.11 ± 0.15 SD with range (1.85 – 2.55). Similar results were reported by **Barbagallo *et al.*** [15] who identified magnesium ion was significantly lower in the AD group as compared to age-matched control adults without AD. **Ben Zaken *et al.*** [16] described that there were significantly more cases with low magnesium levels among dementia patients than among controls with 9.4% of tests done in patients with dementia and 7.81 done in non-dementia subjects were hypomagnesaemia ($p < 0.00001$).

We conducted a correlation analysis between serum magnesium levels and cognitive function assessment score tests, and there was statistically significant correlation between magnesium and MoCA test parameters in abnormal group (Visuspatial/executive, attention, language, delay recall and score), also Mini mental state examination parameters in abnormal group (Orientation, recall, language and score) besides the Recall Mini-COG test in abnormal group. We supported **Basheer *et al.*** [3] in their sample of elderly participants, found a significant association between increased magnesium levels and higher cognitive function scores.

In our study we revealed that there was a high statistically significant association between the two studied groups (normal and abnormal cognitive functions) and phosphorus. The mean phosphorus in abnormal cognitive functions group 4.24 ± 0.71 SD with range (1.76 – 5.10) was higher the mean phosphorus in normal cognitive functions group 3.55 ± 0.48 SD with range (2.60 – 4.56). These findings were comparable and consistent with **Li *et al.*** [6] who concluded higher serum phosphorus levels, even if in the normal range, are associated with increased risk of incident dementia, the association is more robust in those younger than 60 years old.

In the correlation analysis between serum phosphorus levels and cognitive function assessment score tests that, MoCA test parameters in abnormal group (Visuspatial/executive, attention, language, abstraction, delay recall and score), besides Mini mental state examination in abnormal group (Orientation, recall and score) and Recall Mini-COG test in abnormal group. Also, there was statistically significant correlation between phosphorus and age in abnormal cognitive functions group.

There was statistically significant correlation between phosphorus and age in abnormal cognitive functions group, ALT, AST, and age in normal group, andbWBC, Hgb, PLT, total bilirubin, direct bilirubin,

ALT and AST in abnormal group. Unlike **Daniluk [17]** who did not observe any significant associations between higher fasting serum phosphorus levels and odds of cognitive impairment when combining men and women, also no association was found between higher serum phosphorus levels and lower verbal and visual memory scores or increased odds of cognitive impairment on those scores. To our knowledge, no other studies have examined the association between measured serum phosphorus levels and cognitive performance on verbal or visual memory tests. These covariates have been previously shown to be physiologically related and have very significant modifying effects on each other, thus making it imperative to adjust for in an analysis.

In order to identify the factors affecting cognitive function, multiple regression analysis was performed with age, education, the laboratory blood levels, MoCA, and MMSE scoring tests as independent variables. As a result of conducting linear and multiple regression analysis by entering variables by a stepwise method, it was found that the odds of abnormal cognitive increased with age (OR: 1.251, CI 95%: 1.035 – 1.512, $p < 0.021$), ALT and AST (OR: 1.147, CI 95%: 1.051-1.252) and (OR: 1.177, CI 95%: 1.096-1.265) respectively. Also, it was found that the odds of abnormal cognitive increased with Visuspatial/ executive MoCA, Language MMSE, Mg and P^{3+} (OR: 6.355, CI 95%: 2.739-14.741). **Lee and Kim [18]** conduct multiple regression analysis and found that age (β=-.21, p=.016) and education (β=.43, p<.001) had a significant effect, and the regression model was statistically significant (F=21.05, p<.001). They also agreed our analysis indicating that calcium was not an independent factor with cognitive impairment. **Daniluk [17]** also agreed with our model and revealed in particular, the odds of cognitive impairment increased at levels of phosphorus above 3.5 mg/dL.

CONCLUSION

The results of our study give us an expression that macronutrients such as calcium, magnesium and phosphorus may be associated with cognitive function in elderly population. Calcium and magnesium are associated with cognitive improvement in elderly, but in contrast, higher level of phosphorus facilitates cognitive decline. We concluded that age, magnesium and phosphorus were independent variable for cognitive impairment.

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