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STUDY OF THE ASSOCIATION BETWEEN COGNITION AND LEVELS OF CYSTATIN C IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT
Chronic kidney disease (CKD) is a common clinical problem in elderly patients. Serum cystatin C is protein which suggested to be an ideal marker of GFR. CKD is a risk factor for dementia. We aimed to determine the serum levels of Cystatin C in patients with CKD and to correlate this with degree of cognitive impairment and stages of kidney disease. 90 subjects aged 65 years and older were involved, divided into two groups; Group (I): 60 patients with CKD, and Group (II): 30 age and sex matched healthy participants. Patients with heart failure, hepatic failure, thyroid disease, patients underwent dialysis for longer than 1 month, patients had polycystic kidney disease, who had bone marrow transplant, and those receiving immunosuppressive therapy with in the past 6 months were excluded from the study. Mini-Mental scale (MMS), serum cyctatin level, stage of CKD were done to all participants. Serum Cystatin level was significantly high in CKD patients. MMS score was significantly lower in CKD patients. A high significant negative correlation was found between serum Cystatin C levels and degree of cognitive impairment. Also a significant positive correlation was found between levels of cognitive impairment and GFR. A high significant negative correlation was found between serum Cystatin C levels and GFR (R=-0.531, p <0.001).we concluded that serum Cystatin levels are significantly associated with cognitive impairment in CKD patients, and this correlation becomes stronger with advanced stages of CKD. That may help in better understanding of the pathogenesis of dementia in CKD patients.

KEYWORDS: Dementia, cognitive impairment, Cyctatin C, chronic kidney disease, elderly.

INTRODUCTION
Chronic kidney disease (CKD) is a common clinical problem in elders and is associated with increased morbidity and mortality.[1] The prevalence of CKD increases with age with the highest prevalence in elderly.[2] The prevalence of CKD in Egypt is estimated to be 650 per million (pmp).[3] The new definition of CKD depends on estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m2 for at least 3 months, and abnormal renal markers as proteinuria, abnormal radiology, abnormal cells in the urine, renal pathology on biopsy, or a history of renal transplantation.[4] CKD is classified into five stages, from kidney disease with a preserved GFR with GFR is >90 ml/min, to end-stage kidney failure with GFR <15 ml/min.[5] Hypertension and diabetes mellitus are among the most important risk factors for CKD.[5]

Serum cystatin C is a non-glycosylated, 13.3-kDa protein belonging to cystatin protease inhibitors encoded by the CST3 gene.[6] Cystatin C has the advantage over creatinine that, it is not affected by renal conditions, protein metabolism, diet, age, or muscle mass. It is filtered in the renal glomeruli, and reabsorbed by the proximal tubule. So, cystatin C has been suggested to be an ideal endogenous marker of GFR.[7] CKD and cognitive impairment commonly occur in elders, yet the relation between CKD and cognitive function remains poorly understood. Cystatin C has been studied as a measure of kidney function and as a biomarker of cognitive impairment.[8] Cystatin-C colocalizes with β-amyloid in brains of patients with Alzheimer disease (AD).[9] Several studies have reported an association between a common polymorphism of the cystatin-C gene and risk of AD.[10]

Cognition relates to various brain functions as attention, language, memory, learning, reasoning, decision making, and problem solving. Cognitive impairment is defined as a decline in patient's baseline functions to a level severe enough to interfere with his daily activities.[11] The incidence of dementia is about 7.7 million per year, and mild cognitive impairment is even more prevalent.[12] CKD is a risk factor for cognitive impairment.[13] Cognitive impairment is a risk factor for dialysis-related mortality.[14]

Higher levels of cystatin C are associated with increased risk of mortality, cardiovascular events, and poor quality of life,[15] and in patients with CKD, it better predicts kidney progression to ESRD.[16] Although individuals with CKD are also at high risk for cognitive impairment,[17] using cystatin C as a marker of poor cognitive performance in those patients has not been fully investigated.[18] We aimed in the current study to evaluate the level of serum Cystatin C levels in patients with chronic kidney disease and to correlate these values with degree of cognitive impairment and stages of kidney disease.

MATERIALS AND METHODS

The present study included 90 subjects aged 65 years and older, who attended the outpatient clinics in Sharq El Madina Hospital. They are divided into two groups; Group (I): 60 patients with chronic kidney disease, and Group (II): 30 age and sex matched healthy participants who attended ophthalmology and dermatology outpatient clinics, served as a control group. The aim, purpose, and benefits of the study were explained to all participants and an informed written consent was obtained. The proposal was accepted by the ethical committee of faculty of medicine-Alexandria University. Patients with chronic kidney disease with GFR less than 60 ml/min/1.73 m2 were included in the study. Participants with the following conditions were excluded from the study; heart failure and hepatic failure, thyroid disease, patients underwent dialysis for longer than 1 month, patients had polycystic kidney disease, who had organ or bone marrow transplant, and those receiving immunosuppressive therapy with in the past 6 months. All participants were subjected to a thorough history taking, full clinical examination, and routine laboratory investigations including thyroid function testes. Serum levels of Cystatin C was determined to all participants using ELISA kits.[19] Cognitive impairment was diagnosed according to the mini-mental state scale.[20] Mini-Mental scale includes 11-questions measure five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment.

Data were collected and fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median.

Significance of the obtained results was judged at the 5% level. Chi-square test was used for categorical variables, to compare between different groups. Student t-test was used for normally quantitative variables, to compare between two studied groups. Mann Whitney test was used for abnormally quantitative variables, to compare between two studied groups .Spearman coefficient was used to correlate between two abnormally quantitative variables.

RESULTS

The present study included 90 participants aged 65 years and older, divided into two groups; Group (I): included 60 elderly patients with different degrees of renal impairment with a mean age of 68.80 ± 5.74 years, and group (II) included 30 elderly healthy subjects served as a control group with a mean age of 66.90 ± 3.25 years. There was no significant statistical difference between the two studied groups (p=0.048). Group (I) included 40 females (66.7 %), and 20 males (33.3%), while group (II) included 11 females (36.7%), and 19 males (63.3%), with a statistically significant difference between the two studied groups (p=0.007).

Regarding values of random blood glucose (RBG). The mean value of RBG in group (I) was158.15 ± 71.21mg/dl, while it was 100.43 ± 9.75 mg/dl in group (II), levels were significantly higher in group I (p<0.001).

Regarding renal function parameters. The mean value of urea in group (I) was 79.25 ± 36.52 mg/dl, while it was 32.50 ± 13.53 mg/dl in group (II), with a high statistical significant difference between both groups (p<0.001). The mean creatinine level in group (I) was 1.64 ± 0.34 mg/dl, While in group (II) was 0.62 ± 0.19 mg/dl, with a high statistical significant difference between both studied groups (p<0.001). The mean uric acid level in group (I) was 6.98 ± 1.91 mg/dl, while it was 4.30 ± 1.18 mg/dl in group (II), a high statistical significant difference between both groups (p<0.001).

In group (I), 27 patients (45%) had no protein in their urine, 12 patients (20%) had 1+ protein, 6 patients (10%) had 2+ protein, and 15 patients (25%) had 3+ protein. In group II, 22 subjects (73.3%) had nil protein in their urine, 8 subjects (26.8%) had 1+ protein, while no one had either 2+ or 3+ protein. A high statistical significant difference was found between both groups (p=0.001).

In group I, only one patient (1.7%) had granular casts, another one patient (1.7%) had uric acid crystals, and another two patients (3.3%) had calcium oxalate crystals, while 56 patients (93.3%) had no casts. In group II, only one subject (3.3%) had calcium oxalate crystals while 29 subjects (96.7%) had no crystals. No statistical

significant difference was found between both groups (p=1.00).

Table 1 represents a Comparison between the two studied groups regarding the Grades of Chronic Kidney Disease (CKD), and Glomerular filtration Rate (GFR). In group (I) , the mean GFR was 36.12 ± 10.15(ml\min\1.73) , 37 patients (61.7%) were stage III chronic kidney disease , and 23 patients (38.3%) were grade IV , while no patients were in stages I, II or V. In group (II), the mean GFR was 135.87 ± 32.46 (ml\min\1.73), 30 subjects (100%) were stage I CKD. A high statistical significant difference was found between both groups (p<0.001).

Table 1: Comparison between the two studied groups regarding Grades of Chronic Kidney Disease (CKD) and Glomerular filtration Rate (GFR):

	Patients Group I (n=60)		Control group Group II (n=30)		Test of sig.	P
	No.	%	No.	%		
Grades of CKD						
Stage I (≥ 90)	0	0.0	30	100.0	χ^2= 85.645*	<0.001*
Stage II (60 – 89)	0	0.0	0	0.0		
Stage III (30 – 59)	37	61.7	0	0.0		
Stage IV (15 – 29)	23	38.3	0	0.0		
Stage V (<15)	0	0.0	0	0.0		
GFR (ml\min\1.73)						
Min. – Max.	20.0 – 54.0		96.0 – 223.0		t= 16.434*	<0.001*
Mean ± SD.	36.12 ± 10.15		135.87 ± 32.46			
Median	37.50		123.0			

χ^2, p: χ^2 and p values for Chi square test for comparing between the two groups.
t, p: t and p values for Student t-test for comparing between the two groups.
*: Statistically significant at p ≤ 0.05.

Table 2 represents a Comparison between the two studied groups regarding serum Cystatin C level (mg\l). The mean value of serum Cystatin in group (I) was 1.83 ± 0.87 mg/L, while in group (II) was 1.15 ± 1.25 mg/L , with a statistical significant difference between both studied groups (p=0.004).

Table 2: Comparison between the two studied groups regarding Serum Cystatin C level:

	Patients (n=60)	Control (n=30)	t	P
Serum Cystatin C level (mg\l):				
Min. – Max.	0.43 – 4.26	0.36 – 7.58	2.998*	0.004*
Mean ± SD.	1.83 ± 0.87	1.15 ± 1.25		
Median	1.77	0.86		

t, p: t and p values for Student t-test for comparing between the two groups.
*: Statistically significant at p ≤ 0.05.

Table 3 represents a Comparison between the two studied groups regarding results of mini mental scale. In group (I), 14 patients (23.3%) had normal cognitive function, 18 patients (30%) had mild cognitive impairment, 28 patients (46.7%) had moderate cognitive impairment, and no one had severe cognitive impairment. In group (II), 14 patients (46.7%) had normal cognitive impairment, 12 patients (40%) had mild cognitive impairment, 4 patients (13.3%) had moderate cognitive impairment, and no one had severe cognitive impairment. A statistical significant difference was found between both studied groups (p=0.006). The mean value of mini mental scale was 19.72 ± 4.63 in group (I), while it was23.47 ± 3.97 in group (II). A high statistical significant difference was found between both studied groups (p<0.001).

Table 3: Comparison between the two studied groups regarding the Mini Mental Scale:

	Patients Group I (n=60)		Control group Group II (n=30)		Test of sig.	P
	No.	%	No.	%		
Grades of Mini Mental						
Normal (25 – 30)	14	23.3	14	46.7	χ^2= 10.350*	0.006*
Mild (20 – 24)	18	30.0	12	40.0		
Moderate (10 – 19)	28	46.7	4	13.3		
Severe (< 10)	0	0.0	0	0.0		
Mini Mental scale:						
Min. – Max.	10.0 – 28.0		12.0 - 30.0		t=3.794*	<0.001*
Mean ± SD.	19.72 ± 4.63		23.47 ± 3.97			
Median	20.0		24.0			

χ^2, p: χ^2 and p values for Chi square test for comparing between the two groups.
t, p: t and p values for Student t-test for comparing between the two groups.
*: Statistically significant at $p \leq 0.05$.

Table 4 represents the distribution of patients with different grades of CKD regarding results of Mini Mental Scale. 37 Patients were in stage III CKD, of them, 13 patients (92.9%) had normal cognitive functions, 14 patients (77.8%) had mild cognitive impairment, and 10 patients (35.7%) had moderate cognitive impairment. 23 patients were in Stage IV CKD, of them, one patient (7.1%) had normal cognitive function, 4 patients (22.2%) had mild cognitive impairment, and 18 patients (64.3%) had moderate cognitive impairment. A high statistical significant difference was noted between both groups (p<0.001).

Table 4: Distribution of patients with different grades of CKD regarding results of Mini Mental Scale:

Grades of CKD	Mini Mental Scale						χ^2	p
	Normal (25 – 30) (n=14)		Mild (20 – 24) (n=18)		Moderate (10 – 19) (n=28)			
	No.	%	No.	%	No.	%		
Stage III (30 – 59)	13	92.9	14	77.8	10	35.7	15.716*	<0.001*
Stage IV (15 – 29)	1	7.1	4	22.2	18	64.3		

χ^2, p: χ^2 and p values for Chi square test
*: Statistically significant at $p \leq 0.05$.

Table 5 shows the correlation between different studied parameters in patients in Group (I). A high significant negative correlation was found between serum Cystatin C levels and degree of cognitive impairment represented by Mini Mental Scale (R=-0.444, p<0.001). Also a significant positive correlation was found between degree of cognitive impairment and glomerular filtration rate (R= 0.325, p=0.011). A high significant negative correlation was found between serum Cystatin C levels and Glomerular filtration rate (R=-0.531, p <0.001).

Table 5: Correlation between different parameters in Group (I):

	R	P
Mini Mental examination VS serum Cystatin C level	-0.444*	<0.001
Mini Mental examination VS GFR	0.325*	0.011
Serum Cystatin C level VS GFR	-0.531*	<0.001

r: Pearson coefficient
*: Statistically significant at $p \leq 0.05$.

DISCUSSION

Cognitive impairment is one of the costliest disabilities, making successful aging without cognitive impairment a paramount goal for society.[21] Kidney diseases are highly prevalent in the elderly,[22] and they are associated with many adverse health outcomes.[23] Many studies have reported the association between poor kidney function, and cognitive impairment in older adults.[24] Cystatin C, has been studied as a measure of kidney function and as a biomarker of cognitive impairment.[8] In some community-based cohort studies, high levels of cystatin C were associated with increased risk of cognitive impairment,[25] while in other observational studies, low levels of cystatin C was associated with greater risk of dementia.[26] Although individuals with CKD are also at high risk for cognitive decline and dementia,[17] the potential of cystatin C as a marker of

poor cognitive performance in this population has not been fully investigated. We aimed in the current study to determine the association of serum levels of Cystatin C, and cognitive impairment in patients with CKD.

Our results revealed significantly higher levels of serum Cystatin C in elderly patients with CKD compared to control group participants. A high significant negative correlation was found between serum Cystatin C levels and degree of cognitive impairment represented by Mini Mental Scale. Also a significant positive correlation was found between the degree of cognitive impairment and the degree of renal impairment. A high significant negative correlation was found between serum Cystatin C levels and eGFR.

Possible explanations for our findings; that association between CKD and cognitive impairment include increases in cardiovascular disease and inflammation. Cystatin-C has been found to correlate highly with subclinical brain infarcts in elders,[27] while we adjusted for cardiovascular disease risk factors as hypertension, BMI and stroke and the association between cystatin-C level and cognition remained. Cystatin-C is produced by nearly all human cells and cystatin-C colocalizes with β-amyloid in brains of patients with AD.[28] Many studies have reported an association between a common polymorphism of the cystatin-C gene and risk of AD suggesting that cystatin-C may have a direct effect on AD risk.[29] Supporting this possibility, when we used eGFR cutoffs used to classify CKD, elders with high cystatin-C had higher risks of cognitive impairment.

In agreement with our findings, a prospective study by Yaffe K et al.[30] that enrolled 3075 community-resident elders, those with elevated cystatin-C had lower scores on cognitive tests and, participants with elevated cystatin-C were approximately twice as likely to develop cognitive impairment. They also stated that relative to serum creatinine or creatinine-based equations, cystatin-C concentrations may represent a more sensitive marker of CKD, particularly in the elderly.

Also in agreement with our results, A study by Kurella M et al,[31] done on 1,015 post-menopausal women who underwent 6 standard tests of cognitive function evaluating various domains. eGFR was associated significantly with impairment in global cognition, executive function, language, and memory . Associations among eGFR and cognitive function were independent of residual effects of age and race, the two key determinants of GFR and the contributions of education, lifestyle factors, stroke, diabetes, and other laboratory variables.

A study by Yaffe K et al,[18] which enrolled 821 participants with mean age of 64.9 years, 50.6% of them were male. They found that after multivariable adjustment for age, race, education, and medical comorbidities in linear models, higher levels of cystatin C were associated with worse cognition. This association was independent of eGFR levels.

Sarnak MG et al,[26] studied 2140 participants with mean age of 74 years. After a 6-year follow-up in the Cardiovascular Health Study, a community-based cohort of older adults (aged >or= 65 years), the highest vs lowest quartile of cystatin C was independently associated with incident cognitive or physical disability.

High levels of cystatin C have also been associated with increased presence of subclinical brain infarcts,[32] and in a recent cohort study of older adults, markers of kidney function, including elevated cystatin C levels, were associated with poor global cognition and increased white matter deficits in the anterior limb of the internal capsule,[33] a region associated with impairment on executive function and episodic memory.[34]

The association between cystatin C and cognitive function in our study could be related to vascular pathology and share pathways with cardiovascular outcomes also linked to cystatin C including hypertension, obesity, and coronary heart disease.[8]

Slinin Y et al,[35] conducted a longitudinal analysis of a prospective cohort of 1,332 community dwelling elderly women without dementia at baseline who had baseline cystatin C and serum creatinine measurements and completed an extended cognitive battery of neuropsychological tests with determination of cognitive status 10 years later. Incident cognitive impairment was defined as either new onset of adjudicated diagnosis of mild cognitive impairment or dementia. Their results support a U-shaped association between cystatin C concentration and risk of cognitive impairment or dementia 10 years later, but the association is not independent of potential confounding factors.

In contrast to our results, Serum cystatin C levels were measured at two visits 7 years apart in the Uppsala Longitudinal Study of Adult Men,[36] a community-based study of elderly men who were followed for 11.3 years for development of Alzheimer's disease. Lower levels of cystatin C were associated with higher risk of Alzheimer's disease independently of other covariates.
In another study, cystatin C level below the median (<1,067ng/mL) in patients with mild cognitive impairment was associated with greater incidence of Alzheimer's dementia at 2.5 years follow-up.[37]

Kálmán J, et al,[38] examined the serum and cerebrospinal fluid cystatin C levels of 24 late onset Alzheimer's demented (AD) and 16 ischemic type of vascular demented probands compared with 17 aged control persons. The serum and CSF cystatin levels were found in the normal range in all groups. The ischemic VD probands had the tendency to have higher cystatin C levels than the AD. No correlation has been found with the severity and duration of dementia and with the other

measured parameters. The small study sample may be the reason for this findings.

IN CONCLUSION

Our study found that high cystatin C levels were associated with greater likelihood of poor cognitive performance in older adults with CKD. Although the sample size was small, and we could not examine all cognitive domains, the findings are preliminary, additional longitudinal studies are needed to determine the potential role for cystatin C as a biomarker for cognitive decline and to determine the mechanisms underlying this association.

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