Evaluation of the Prevalence of Silent Cerebral Infarction among Neurologically Free Chronic Kidney Disease Patients

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Abstract: Objectives: To evaluate the prevalence of silent cerebral infarction (SCI) among neurologically free chronic kidney disease (CKD) patients as judged by brain MRI examinations. **Patients & Methods:** The study included 230 CKD patients; 165 males and 65 females with mean age of 58±7.9 years. Seventy-six patients (34%) had ischemic heart disease (IHD), 34 patients (14.8%) with non-ischemic heart diseases (Non-IHD), 196 patients (85.2%) had diabetes mellitus (DM), 173 patients (75.2%) were hypertensive patients and dyslipidemia was detected in 185 patients (80.4%). All patients underwent categorization according estimated glomerular filtration rate (eGFR) and all underwent MRI examination. **Results:** Brain MRI defined SCI in 117 patients for a prevalence rate 50.9%. The frequency of patients had SCI was significantly higher in older patients with significantly higher mean age of those had SCI compared to those had MRI free of SCI. The presence of SCI showed positive significant correlation with age (r=0.278, p<0.01), but showed a negative significant correlation with eGFR, (r=-0.249, p=0.001). The frequency of cardiac patients among those had CKD was significantly higher compared to non-cardiac patients with non-significant difference according to presence of ischemia. The frequency of diabetics among CKD patients was significantly higher compared to non-diabetics with significant prevalence among CKD patients with SCI. The frequency of hypertensive patients among CKD patients was significantly higher compared to normo-tensive patients with significantly higher frequency of hypertensive patients among patients had SCI. However, the frequency of dyslipidemic patients among CKD with or without SCI was non-significant. **Conclusion:** The frequency of SCI as judged by brain MRI was high among neurologically free CKD patients especially the older one and if associated with IHD, type-2 DM and/or hypertension. Also, such frequency was negatively correlated eGFR as a measure for renal function.

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1. Introduction

Silent cerebral infarction (SCI) is defined as a brain lesion that is presumably a result of vascular occlusion found incidentally by magnetic resonance imaging (MRI) or computed tomography (CT) in otherwise healthy subjects or during autopsy. The presence of preclinical cerebral microvascular disease as white matter hyperintensities (WMHs), silent lacunar infarcts (LACs), and/or brain microbleeds (BMBs), suggests small-vessel disease involvement, ***(Lee et al., 2000, Vermeer et al., 2007)***.

The reported prevalence of SCI has been varied, depending on the study subjects. In studies dealing with symptomatic stroke patients, the prevalence ranged from 10% to 38%, a prevalence of 13% was reported in a small population study of normal subjects,6 and in a study on a large number of elderly subjects, the prevalence was 33% in patients >65 years. Collectively, it has been reported that the prevalence of SCI in the general population was from 8% to 28%, with the differences mainly explained by age, ***(Lee et al., 2000)***.

The presence of SBI can predict clinical overt stroke and progressive brain damage that may be associated with reduced cognitive function or vascular dementia. In most cases, SCI is found as a lacunar infarction that is a small, deep cerebral infarction caused by occlusion of small penetrating cerebral arteries. Therefore, SBI is categorized as small vessel disease and thus differs from other cardiovascular disease, such as ischemic heart disease, aortic dissection and atherothrombotic cerebral infarction, because they are categorized as large vessel disease, ***(Vermeer et al., 2003)***.

Several studies, in both population- and patient-based cohorts, have demonstrated a strong

association between increased aortic pulse wave velocity and excess risk of cardiovascular complications, including stroke. Cerebral microvascular disease results from the damaging forces of abnormal flow pulsations extending into small cerebral arteries as a consequence of arterial stiffening, ***(Laurent et al., 2003, Mattace-Raso et al., 2006)***.

Poor kidney function is highly prevalent in the general elderly population. It often remains subclinical and is then only identified by measuring a decreased glomerular filtration rate (GFR). Poor kidney function is associated with features of large vessel disease, such as hypertension, arterial stiffness, and ischemic heart disease. Moreover, kidney dysfunction is also characterized by glomerular endothelium dysfunction and lipohyalinosis, both of which are features of small vessel disease in the kidney. In the elderly, small vessel disease is also abundantly present in the brain. Given the hemodynamic similarities between the vascular beds of the kidney and the brain, small vessel disease in the kidney may be indicative of presence of small vessel disease in the brain, ***(Schiffrin et al., 2007, Ochi et al., 2009)***.

However, data on the relationship between kidney function and MRI-markers of cerebral small vessel disease are scarce, so the current prospective comparative study aimed to evaluate the predictability of altered clinical and laboratory renal function data and presence of SCI on brain MRI examination.

2. Patients and Methods

The present study was conducted at Departments of Neurology & Nephrology, Al-Dar Hospital, Quba, KSA since Jan 2009 till March 2011. The study included 300 patients with chronic renal disease (CRD). CRD was defined as either kidney damage or Glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 or more months. Kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies ***(NKF.K/DOQI, 2002)***.

Glomerular filtration rate (GFR) for creatinine was calculated according to Modification of Diet in Renal Disease Study Group as follows: eGFR= (186xserum creatinine)-(1.154xAge-0.203)x(1.21 if black)x(0.742 if female) and CRD staging based on eGFR was as follows: Stage I or 2 if GFR was 51-59 ml/min/1.73 m^2, Stage 3 if GFR ranged between 30–50 ml/min/1.73 m^2, Stage 4 if GFR ranged between 15–29 ml/min/1.73 m^2 and Stage 5 if GFR was <15 ml/min/1.73 m^2, **(NKF.K/DOQI, 2002)**.

All patients underwent clinical history taking and clinical examination including measurement of body mass index (BMI) which equals weight (kg) divided by height in m^2, **(Garrow, 1990)**, blood pressure measurements and inquiry about associated morbidities and risk factors. Blood samples were collected after an overnight fast for the determination of serum creatinine, hemoglobin, fibrinogen, total protein, albumin and lipid profile, all laboratory investigations were conducted at Hospital Lab.

MRI was performed with a 1.5 Tesla MRI unit (Sigma, General Electric Co). SCI lesions were defined as high-intensity areas identified on a T2-weighted image coinciding with low-intensity areas on a T1-weighted image. Patients were categorized according to the presence of SCI into two groups: SCI group included patients had SCI lesions and Non-SCI group included those without any lesions.

3. Results

The study included 230 CRD patients; 165 males and 65 females with mean age of 58±7.9; range: 43-72 years. Only 57 patients (24.8%) had never smoked; 132 patients (57.4%) were ex-smokers, while 41 patients (17.8%) were still smokers.

Clinical evaluation detected 76 patients (34%) with ischemic heart disease (IHD), 34 patients (14.8%) with non-ischemic heart diseases (Non-IHD) and 120 patients (52.2%) had no cardiac lesion. Thirty-four patients (14.8%) were normoglycemic, while 196 patients (85.2%) were diabetics; 114 patients (49.6%) were type-2 diabetics and 82 patients (35.7%) were type-1 diabetics. Only 57 patients (24.8%) were normotensive, while the other 173 patients (75.2%) were hypertensive patients. Lipid profile evaluation defined 185 dyslipidemic patients (80.4%), while 45 patients (19.6%) had normal lipid profile. Patients' enrolment data are shown in table 1.

Mean eGFR was 32.5±16.7; range: 7.5-58 ml/min/1.73 m^2. Sixty patients (26.1%) were CKD stage V, 44 patients (19.1%) were stage IV, 69 patients (30%) were stage III and 57 patients (24.8%) were stages I-II, (Fig. 1). Brain MRI defined SCI in 117 patients of the studied 230 patients for a general prevalence rate 50.9%, (Fig. 2). The frequency of patients had SCI was significantly higher in older patients than in younger ones with significantly higher mean age of those had SCI compared to those had MRI free of SCI, (Fig. 3). The presence of SCI showed positive significant correlation with age (r=0.278, p<0.01), but showed a negative significant correlation with eGFR, (r=-0.249, p=0.001).

Despite the significantly (p<0.05) higher frequency of males among patients with CKD

compared to females, male gender showed non-significantly (p>0.05) higher frequency between patients with or free of SCI. The frequency of cardiac patients among those had CKD was significantly (p<0.05) higher compared to non-cardiac patients, but patients with IHD were non-significantly (p>0.05) frequent among cardiac patients had SCI compared to those had non-IHD. Similarly, the frequency of diabetics among CKD patients was significantly (p<0.05) higher compared to non-diabetics, and the frequency of diabetics CKD patients with SCI was significantly (p<0.05) higher compared to those free of SCI. The frequency of hypertensive patients among CKD patients was significantly (p<0.05) higher compared to normo-tensive patients with significantly (p<0.05) higher frequency of hypertensive patients among patients had SCI. However, the frequency of dyslipidemic patients among CKD was non-significantly (p>0.05) higher with non-significantly (p>0.05) higher frequency of dyslipidemia among those had SCI, (Table 2).

Table (1): Patients' constitutional data

Data			Findings
Age (years)	Strata	40-50	50 (21.7%)
		>50-60	96 (41.7%)
		>60-70	78 (34%)
		>70	6 (2.6%)
	Total	58±7.9 (43-72)	230 (100%)
Gender	Males		165 (71.7%)
	Females		65 (28.3%)
Anthropometric data	Weight (kg)	97.2±6.1 (69-114)	
	Height (cm)	169.4±5.9 (160-178)	
	BMI (kg/m^2)	34±2.7 (25.7-41.5)	
Smoking	Never smoked		57 (24.8%)
	Ex-smoker		132 (57.4%)
	Still smoker		41 (17.8%)
Associated co-morbidities	Heart diseases	Ischemic heart disease	76 (33%)
		Non-ischemic heart disease	34 (14.8%)
		Non-cardiac	120 (52.2%)
	Diabetes mellitus	Type-1 DM	82 (35.7%)
		Type-2 DM	114 (49.5%)
		Non-diabetic	34 (14.8%)
	Hypertension	Hypertensive	173 (75.2%)
		Normo-tensive	57 (24.8%)
	Lipid profile	Dyslipidemia	185 (80.4%)
		Normal	45 (19.6%)

Data are presented as mean±SD & ratios; ranges are in parenthesis

Table (2): Patients' distribution according to presence of SCI categorized according to age, gender and associated co-morbidities

			SCI (n=117)	Free (n=113)	
Age (years)	Strata	40-50	18 (15.4%)	35 (31.1%)	X^2=8.174, p<0.01
		>50-60	41 (35%)	50 (44.2%)	
		>60-70	54 (46.2%)	24 (21.2%)	
		>70	4 (3.4%)	4 (3.5%)	
	Total		60.1±7.6 (43-72)	55.7±8 (44-71)	Z=3.746, p<0.001
Gender	Males		85 (72.6%)	80 (70.8%)	X^2=31.478, p<0.001
	Females		32 (27.4%)	33 (29.2%)	
Cardiac disease	Ischemic heart disease		42 (35.9%)	34 (30.1%)	X^2=2.114, p>0.05
	Non-ischemic heart disease		24 (20.5%)	10 (8.8%)	
	Total cardiac patients		66 (56.4%)	44 (38.9%)	X^2=3.339, p <0.05
	Non cardiac		51 (43.6%)	69 (61.1%)	
Diabetes mellitus	Type-1 Diabetes mellitus		34 (29.1%)	48 (42.4%)	X^2=6.142, p <0.05
	Type-2 Diabetes mellitus		75 (63.7%)	39 (23.1%)	
	Total diabetics		109 (92.8%)	87 (65.5%)	X^2=3.481, p <0.05
	Non diabetic		8 (7.2%)	26 (34.5%)	
Hypertension	Hypertensive		102 (87.2%)	71 (62.9%)	X^2=6.294, p <0.01
	Normo-tensive		15 (12.8%)	42 (37.1%)	X^2=7.47, p <0.01
Lipid profile	Dyslipidemic		96 (82.1%)	89 (78.8%)	X^2=0.296, p >0.05
	Non-dyslipidemic		21 (17.9%)	24 (21.2%)	X^2=0.421, p >0.05

Data are presented as mean±SD & ratios; ranges are in parenthesis

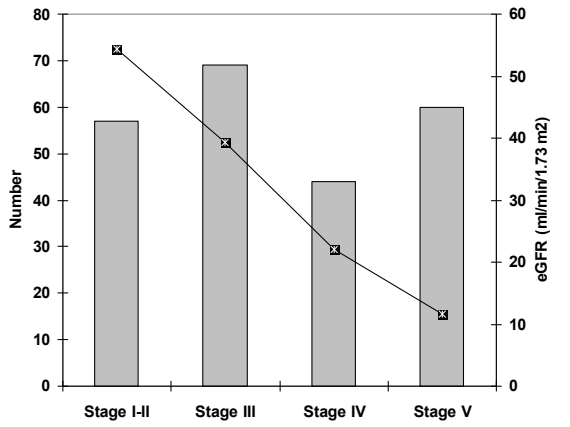

Fig. (1): Patients distribution according to CKD stage and mean eGFR

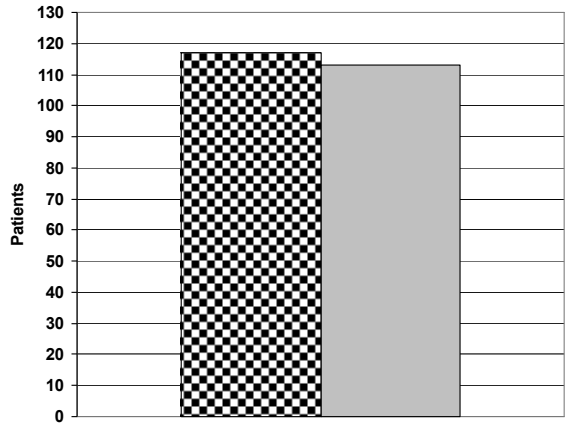

Fig. (2): Patients' distribution according to MRI evidence of SCI

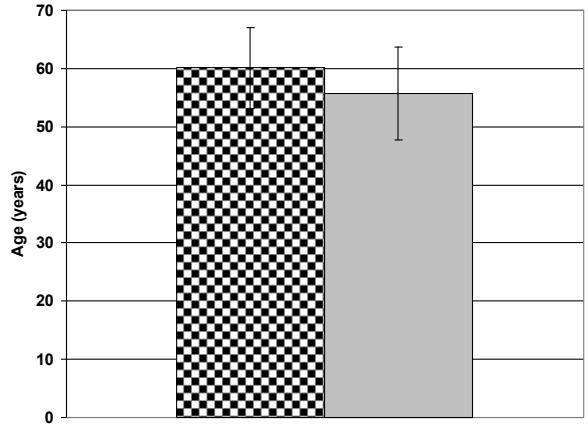

Fig. (3): Mean (±SD) age of patients categorized according to presence of SCI

4. Discussion

Chronic kidney disease (CKD) has been shown to be related to neurological disorders, not only ischemic brain injury but also cognitive impairment. This cerebrorenal connection is considered to involve small vessel disease in both the kidney and brain, based on their hemodynamic similarities. Clinical studies suggest that markers for CKD such as eGFR, proteinuria, and albuminuria may be helpful to predict brain small vessel disease, white matter lesions, silent brain ischemia (SBI), and micro-hemorrhages. Changes in the vascular system of the brain have been shown to contribute to the onset and progression of cognitive impairment, not only vascular dementia but also Alzheimer's disease. Patients with CKD are also reported to have higher risk of impaired cognitive function in the future compared with non-CKD subjects, ***(Mogi & Horiuchi, 2011, Shima et al., 2011)***.

The current study designed on diagnostic screening basis relying on MRI for diagnosis of silent cerebral infarctions in chronic kidney disease patients. Patients' enrollment criteria included being neurologically free without cognitive manifestations to assure screening basis. One-hundred and seventeen patients had MRI findings of SCI, while the remaining 113 patients were MRI free; for a frequency of 50.9% among these series. There was a negative significant correlation between presence of SCI and eGFR with a prevalence rate of 33.3% among Stage I-II CKD and 68.3% among those of grade V. These findings go in hand with that recently reported in literature; ***Vogels et al. (2012)***, found GFR was associated with SCI with 9 out of 12 associations' significant results and indicated that CKD is associated with brain lesions; white matter lesions, SCI and brain atrophy which are predictive of stroke, cognitive decline and dementia. ***Takahashi et al. (2012)***, found the prevalence of asymptomatic cerebral infarction, deep and/or subcortical white matter hyperintensity and periventricular hyperintensity was significantly correlated with degree of eGFR reduction.

Chou et al. (2011) found a close association exists between SBI and eGFR with a significant increase in prevalence of SBI when eGFR is between 30.0 and 44.9 ml/min/1.73 m^2 and concluded that adults with late stage 3 CKD are at high risk for prevalent SBI. ***Shima et al. (2011)***, reported that in CKD patients decreased kidney function is a significant factor associated with silent cerebral lacunar infarction and periventricular hyperintensities, both of which are significantly associated with each other and suggested that CKD patients with SCI are at greater risk of future cerebrovascular events.

The majority of CKD patients with SCI were found to have multiple morbidities with special regard to diabetes mellitus and cardiac diseases. The frequency of diabetics among CKD patients with SCI was significantly higher compared to those free of SCI with significantly higher frequency of type-2

diabetes; a finding indicating that a group of metabolic syndrome patients; diabetics, cardiac, renal patients with definite dyslipidemia are liable to SCI. In support of such assumption, 89.1% of CKD patients with SCI were dyslipidemic. In hand with these data, ***Bouchi et al. (2010a)***, detected SCI in 52.8% of T2DM patients with an eGFR ≥15 ml/min 1.73/m^2 the subjects and the prevalence of SCI was significantly associated with both elevated albumin-to-creatinine ratio and decreased eGFR.

Despite the increased frequency of IHD among CKD patients with SCI (35%), non-ischemic patients also showed a frequency of 23.1% among these patients with a total frequency of cardiac patients of 58.1% of CKD patients with SCI. In line with these findings, ***Kobayashi et al. (2012)***, reported that the number of SCI was significantly larger and the rates of SCI in the cortex/subcortex and deep white matter and grade of deep and subcortical white matter hyperintensity were higher in the non-valvular atrial fibrillation group than in the control group.

The frequency of hypertensive patients among CKD was significantly higher with significantly higher frequency among patients had SCI; a finding indicating a relationship between hypertension and development of SCI. such relationship is still a matter of controversy, ***Shima et al. (2010)*** reported a significant association between the prevalence of cerebral microbleeds (CMBs) and the CKD stage, with higher prevalence of CMBs as the CKD stages advanced, and that estimated GFR was a significant factor associated with the prevalence of CMBs, independent of age, gender and hypertension. On the other side and in hand with the data of the current study, ***Ueda et al. (2011)***, reported that among the 202 patients with ischemic stroke, 27.9% had an eGFR <60 ml/min/1.73 m2, age was significantly higher and a history of hypertension, diabetes, and ischemic heart disease was significantly more frequent in this group than in the group with eGFR ≥60 ml/min/1.73 m^2.

Multiple studies evaluated the relationship between SCI and the development and progression of nephropathy; ***Bouchi et al. (2010b)***, found that in type 2 diabetic patients SCI may be a predictor of progression of nephropathy in type 2 diabetic patients. ***Kobayashi et al. (2010)*** showed that SBI was an important independent prognostic factor for the progression of kidney disease in patients with CKD and patients with SBI should be considered a high-risk population for decreased kidney function. These data illustrate a reciprocal relationship between CKD and SCI indicating a causal-effect relationship warranted through affection of small sized blood vessels. In line with this assumption, ***Yamamoto et al. (2011)*** recommended that renoprotective treatment may be warranted to prevent CI. Also, ***Vogels et al. (2012)***, recommended the need for follow up studies to better understand the causative pathway and to establish whether screening and preventive programs are beneficial.

The obtained results and review of literature allowed to conclude that the frequency of SCI as judged by brain MRI was high among neurologically free CKD patients especially the older one and if associated with IHD, T2DM and/or hypertension. Also, such frequency was negatively correlated eGFR as a measure for renal function. It is recommended to screen CKD patients for the presence of SCI in a trial to institute preventive measures for its progression to frank neurological disease.

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