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ORIGINAL ARTICLE

Reduced glomerular filtration rate as a predictor of coronary artery disease events in elderly patients

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KEYWORDS

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Abstract *Background:* Chronic kidney disease is independently associated with cardiovascular disease (CVD) events in high-risk populations according to several studies. However, findings from community-based population studies are insufficient. We studied the relationship between estimated glomerular filtration rate (eGFR) and risk of coronary artery disease (CAD) events in patients attending Zagazig University Hospital, Sharqiya governorate, Egypt.

Methods: A total of 800 subjects aged ⩾60 years admitted to Internal Medicine Department or attended medicine outpatient clinic were included in this study. Careful history and full clinical examinations were done to assess the risk factors of CAD. Serum creatinine, lipid profile and serum glucose were measured. Estimated eGFR was evaluated by creatinine based MDRD formula. According to eGFR, patients were divided into 2 groups: group 1 with eGFR ⩾ 60 mL/min/1.73 m^2 and Group 2 with eGFR < 60 mL/min/1.73 m (between 40 and 60 mL/min/1.73 m).

Results: 410 patients were found to have eGFR ⩾ 60 mL/min/1.73 m^2, while 390 patients were found to have eGFR < 60 mL/min/1.73 m^2. eGFR was lower in patients with CAD (62 ± 13 mL/min/1.73 m^2) in comparison with patients without CAD (76 ± 11 mL/min/1.73 m^2) ($P \leqslant 0.001$). Older age, hypertension, Diabetes and Low HDL are highly significant risk factors for CAD in those patients (P 0.001).

Conclusions: Reduced eGFR is a significant risk factor for CAD events in older patients. Monitoring of eGFR may have a pivotal role in early detection and management of CAD in those types of patients.

1. Introduction

Chronic kidney disease (CKD) is considered a public health problem.[1] Also, it is a disease entity including mild to end-stage renal diseases due to any etiology.[2] Serum creatinine is generally thought to be a poor indicator of renal function. In contrast, glomerular filtration rate (GFR) is a more accurate measure of renal function.[2] Cardiovascular disease (CVD) is the main cause of mortality in chronic kidney disease patients.[3]

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Previous clinical trials have shown that reduced glomerular filtration rate (GFR) is an independent risk factor for all-cause mortality as well as adverse CVD events, such as myocardial infarction and stroke,[4,5] and patients with a low level of GFR show increased exposure to CVD risk factors, such as diabetes, hypertension and dyslipidemia.[6,7]

Many studies have been restricted to study patients with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 compared to above 60 mL/min/1.73 m.[8–12] However the effects of earlier stages of renal function deterioration on CAD outcomes have been less well studied particularly in the elderly.[13] Thus there is uncertainty as to whether mild renal dysfunction may have adverse cardiovascular effects independent of known risk factors in this population.

In the present study, we hypothesized that eGFR is related to risk of CAD in the general population so we investigated the relationship between reduced estimated GFR (eGFR) and risk of CAD events, either stable or unstable ACS (Acute coronary syndrome), in a community-based sample of elderly patients in Zagazig University Hospital in the period between 2013 and 2015.

2. Methods

2.1. Patient selection

We collected 800 patients attending the outpatient clinic of our hospital for follow-up of their comorbid diseases, during the period from March 2013 to June 2015 to be included in this prospective study.

Inclusion criteria: Patients were considered eligible for enrollment if they were over 60 years of age. Patients were divided into two groups according to eGFR: group 1 with eGFR $\geqslant$ 60 mL/min/1.73 m^2 and group 2 with eGFR between 40 and 60 mL/min/1.73 m^2 as shown in Table 1.

Exclusion criteria: Patients with malignant tumors, bedridden status, mental disorder, and heart and lung failure and patients with advanced chronic kidney disease were excluded from the study before inclusion. An informed written consent was obtained from each patient after full explanation of the study protocol. The study protocol was reviewed and approved by our Local Institutional Human Research Ethical Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Table 1 Baseline characteristics of all study population.

Patient Characteristics	eGFR $\geqslant$ 60 (n = 410) (Group 1)	eGFR (40–60) n = (390) (Group 2)
Age	66 ± 6	69 ± 5
Gender M/F	200/210	341/49
Basal disease		
Angina pectoris (n = 223)	110	113
Old myocardial infarction (n = 168)	77	91
Ischemic cardiopathy (n = 70)	29	41
No CAD (n = 339)	194	145
Risk factor		
Hypertension	127	176
Diabetes mellitus	41	51
Dyslipidemia	180	203

2.2. Clinical and laboratory assessment

Using a pretested questionnaire, information was collected on demographic data, family history of premature CAD, medical history of CAD, drug history, and smoking status. Weight was measured with patients minimally clothed without shoes using digital scales. Height was measured in the standing position without shoes using tape meter while shoulders were in normal alignment. Waist circumference (WC) was measured at the umbilical level and that of the hip at the maximum level over light clothing using an un-stretched tape meter without any pressure to body surface, and BMI was calculated as weight (kg) divided by square of the height (m^2). After a 15-min rest in the sitting position, two measurements of BP were taken on the right arm using a standardized mercury sphygmomanometer and the mean of the two measurements was considered the participant's BP. A blood sample was drawn between 7 AM and 9 AM from all study participants after 12–14 h of overnight fasting. All the blood samples were sent to the laboratory on the day of blood collection. Plasma glucose was measured using an enzymatic colorimetric method with glucose oxidase. Fasting plasma glucose (FPG) measurement was performed for all participants and the standard 2-h post-challenge plasma glucose (2-h PCPG) test for those not taking glucose-lowering drugs. Total cholesterol (TC) was assayed using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid. Triglycerides were assayed using enzymatic colorimetric assay with glycerol phosphate oxidase. Serum creatinine (Cr) levels were assayed by kinetic colorimetric Jaffe method. The sensitivity of the assay was 0.2 mg/dL (range, 18–1330 mmol/L [0.2–15 mg/dL]). GFR was estimated using the Quadratic GFR equation proposed by Rule and colleagues.[14] The estimated GFR calculated in mL/min/1.73 m^2 using the revised "175" Modification of Diet in Renal Disease (MDRD) study equation was: 175 (standardized serum creatinine (Scr) in mg/dL)$^{-1.154}$ × (Age)$^{-0.203}$ × 0.742 with creatinine values entered in mg/dL into the equation.[15]

According to the eGFR, we classified our patients into two groups: group 1 with eGFR $\geqslant$ 60 mL/min and group 2 with eGFR < 60 mL/min/1.73 m^2 (range between 40 and 60 mL/min).

2.3. Diagnosis of coronary artery disease

For the diagnosis of CAD events, we depended on the American Heart Association classification for cardiovascular events[16–18] in addition to pre-tested questionnaire, full medical history and full medical examination. Coronary heart disease (CHD) includes cases of definite myocardial infarction diagnosed by electrocardiography (ECG) and biomarkers (creatine phosphokinase-MB, lactate dehydrogenase, troponin), probable myocardial infarction (positive ECG findings plus cardiac

symptoms or signs and biomarkers showing negative or equivocal results), and unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers).

2.4. Statistical analysis

All quantitative data are presented as mean ± standard deviation (x ± s), and all categorical data are presented as percentages. The differences of these variables among different groups (eGFR > 60, 40–60 mL/min/1.73 m^2) were examined using chi-square statistics for categorical variables and one-way analysis of variance for continuous values. The differences of these variables were compared between subjects with group 1 and group 2 by Student's *t*-test for continuous variables. All data entry and management were performed on Excel spreadsheet and then were analyzed by the SPSS statistical package, version 15.0 (SPSS Inc., http://www.SPSS.com). A *P*-value < 0.05 was considered statistically significant and highly significant if $P < 0.001$.

3. Results

A total of 800 patients were included in our analysis, there were 541 male (67.6%) and 259 female (32.4%) patients, and the age ranged from 60 to 74 years with an average of 65 ± 9 years. 92 patients (11.5%) were diabetic and 303 (37.8%) were hypertensive. According the presence or absence of CAD, patients were classified as angina pectoris ($n = 223$), old myocardial infarction ($n = 168$), Ischemic cardiomyopathy ($n = 70$), and patients without significant CAD ($n = 339$). Table 2 shows a comparison of laboratory, clinical and demographic characteristics in both groups according to the eGFR. There was a significant relationship between both groups according to age, presence of CAD, diabetes and hypertension ($P < 0.001$). Table 3 shows a significant relationship between patients with and without CAD in relation to eGFR ($P < 0.001$). Also there was a significant relationship between both groups according to age and hypertension. Table 4 shows a relation of risk factors in the two eGFR groups. In males the relation of diabetes, hypertension, elevated LDL-C and decreased HDL-C was significantly different in the two eGFR groups and the proportion of risk factor was high in mild renal function group but overweight and high TG were not significantly different in the two eGFR groups. In female patients, the proportion of diabetes, hypertension, overweight, elevated LDL-C and decreased HDL-C was significantly different in the two eGFR groups and the proportion of risk factors increased with the decreasing of the level of eGFR.

Table 2 Laboratory, clinical and demographic characteristics in both groups according to eGFR.

	Group 1 (eGFR ⩾ 60)	Group 2 (eGFR 40–60)	*P* value
Age	66 ± 7	69 ± 5	< 0.001
Male	200 (48.8%)	341 (87.4%)	0.08
CAD patients	215 (52.4%)	259 (66%)	< 0.001
Dyslipidemia	180 (44%)	203 (52%)	0.42
Diabetes	41 (10%)	51 (13%)	< 0.001
Hypertension	127 (31%)	176 (45%)	< 0.001
BMI (kg/m^2)	25.5 ± 3.8	25.8 ± 3.5	0.15
TG (mg/dL)	150 ± 99	145 ± 85	0.52
LDL cholesterol (mg/dL)	101 ± 22	98 ± 25	0.08
HDL cholesterol (mg/dL)	48 ± 12	45 ± 11	< 0.001

Table 3 Comparison of those with and without CAD.

	All participants $n = 800$	CAD $n = 461$	No CAD $n = 339$	*P* value
Age	65 ± 9	69 ± 2	65 ± 4	< 0.001
Hypertension	303 (37.8%)	212 (70%)	91 (30%)	< 0.001
eGFR	75.2 ± 14	62 ± 13	76 ± 11	< 0.001

4. Discussion

In the present study, we have found that prevalence of CAD events in elderly patients with eGFR between 40 and 60 mL/min is more than in population with eGFR > 60 mL/min and also that there was more deterioration of eGFR with increase in age. Renal impairment is considered a major limiting factor for long-term prognosis in CAD patients.[19,20] The risk of death associated with renal dysfunction increases as eGFR declines in previous data in the general population.[21,22] Impaired renal function may increase cardiovascular risk in many ways as renal dysfunction is related to other diseases such as diabetes mellitus and hypertension that themselves have a poorer outcome. In addition to that, renal dysfunction in association with these factors has a markedly worse prognosis. The association between CKD and cardiovascular disease varied based on different cardiovascular risk factor combinations and was highest in those with diabetes.[23] Renal dysfunction might have its harmful effect via pathways independent of other traditional risk factors related to increased CAD risk.[22]

A decreasing GFR is also related to several other factors that affect outcome in cardiac diseases such as impaired left ventricular systolic function and more severe symptoms of heart failure.[24]

This study was designed to explain the clinical significance of eGFR-defined CKD as a predictor of secondary outcomes of CAD. As a result, the eGFR-defined CKD was an independent risk factor for secondary events in patients with CAD.

Regarding a pathophysiological link between CAD and CKD in our results, the increased inflammation and oxidative stress, which have an important role in the pathophysiology of CAD progression, could be associated with poorer renal function. In addition, renal dysfunction may be associated with multiple other physiological changes, including high levels of hypercalcemia, hyperuricemia, homocysteine, anemia, and uremia, all of which have detrimental cardiovascular effects.[25] A previous epidemiological study indicated that CKD patients typically had elevated TG and reduced HDL-C, but no significant alterations in TC and LDL-C.[26] In our study no independent relation was found between BMI and mild renal

Table 4 Relation of risk factors with eGFR levels (mL/min/1.73 m^2) in males and females.

Variable	Male (eGFR(mL/min/1.73 m^2))			Female (eGFR(mL/min/1.73 m^2))		
	⩾60 (n = 200)	40–60 (n = 341)	P value	⩾60 (n = 210)	40–60 (n = 49)	P value
Diabetes	19 (9.5%)	41 (12%)	<0.001	22 (10.47%)	10 (20.4%)	<0.001
Hypertension	90 (45%)	167 (48.9%)	0.32	37 (17.6%)	9 (18.4%)	0.21
BMI ⩾ 25 (kg/m^2)	100 (50%)	177 (51.9%)	0.51	131 (62.3%)	32 (65.3%)	<0.05
TG ⩾ 197.2 (mg/dL)	120 (60%)	219 (64.2%)	0.01	123 (58.5%)	30 (61.2%)	0.02
LDL cholesterol ⩾ 130.3 (mg/dL)	30 (15%)	72 (21.1%)	<0.001	42 (20%)	12 (24.4%)	<0.001
HDL < 40.2 (mg/dL)	33 (16.5%)	77 (22.5%)	<0.001	21 (10%)	8 (16.3)	<0.001

impairment. This may be due to the fact that only morbid obesity (defined as BMI ⩾ 35 kg/m^2) was related to CKD[27] while there were only 21 individuals who had BMI ⩾ 35 kg/m^2 in our study. Also, in this study, elevated LDL-C was shown as an independent risk factor with CKD and reduced renal function. Therefore, lipid-lowering therapy appears to be an important part of CKD management. Certainly, patients with end-stage renal failure have greatly accelerated vascular disease and a high cardiac risk.[28] Thus, kidney function integrates the effects of many factors affecting cardiovascular outcome. Also it has been suggested that, given the effects of vascular disease on kidney function, it may serve as an essential indicator of vascular health.[29] Although the mechanism behind the relation between impaired renal function and the risk of CAD events is not completely understood, several mechanisms have been proposed. Traditional CAD risk factors, such as older age, smoking, hypertension, and dyslipidemia, often coexist with CKD[30–32] and the positive association of these factors with incident CAD is well proved.[33,34] Elevated asymmetric dimethyl arginine, reduced nitric oxide bioavailability, and endothelial dysfunction in kidney disease, which are associated with atherosclerosis, are also defined as factors linking impaired kidney function and the risk of incident CAD.[35,38] In addition, inflammatory markers such as C-reactive protein, fibrinogen, interleukin-6, tumor necrosis factor α, factor VIIc, factor VIIIc, plasmin–antiplasmin complex, D-dimer, the adhesion molecules E-selection, vascular cell adhesion molecule 1, and Intercellular Adhesion Molecule 1 are often elevated. Also, the activation of the renin–angiotensin system, which may depend on the adaptation to loss of renal mass that results in changes in renal hemodynamics, frequently occurs in CKD. These factors may alter the progression of atherosclerosis through their share to the production of reactive oxygen species.[36,37] In addition, increased promoters of calcification and reduced inhibitors of calcification may be responsible for the linkage between kidney impairment and CAD risk.[35,38]

As to eGFR, factors including activation of the renin–angiotensin system, anemia, elevated asymmetric dimethyl arginine, and hyperhomocysteinemia could represent a link between reduced eGFR and increased CAD risk.[36,37]

Our result may reflect the magnitude of the association between kidney function and the risk of incident CAD because kidney function may change over time, potentially affecting their relation with coming CAD events.[39]

The main strengths of our study are its community-based population in Sharqiya governorate, Egypt, and large sample size. The main study limitations are as follows: (1) renal impairment was defined based on a single measurement. The measurements of kidney damage were made just once, and the definition of CKD needs persistence of kidney damage for at least 3 months,[40] which means that, in order to define CKD, indicators of renal impairment should be re-evaluated at least once after 3 months. The single measurement of indicators of CKD in the present study might overestimate the prevalence of CKD. (2) We did not use multivariate analysis to get the different predictors with their odds ratio and confidence interval.

5. Conclusion

We found that reduction of eGFR appears to be a strong predictor as a risk factor for CAD events in our elderly patients. It is possibly related to age-related structural changes in older kidneys due to a reduction in functioning glomeruli. Monitoring of eGFR may have a pivotal role in early detection and management of CAD in those types of patients.

Conflict of interest

No conflict of interest.

Disclosure of grants or other funding

None.

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