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Novel Urinary Biomarkers and Chronic Kidney Disease After Coronary Angiography: A Prospective Case-Controlled Study

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Abstract

BACKGROUND: Novel urinary biomarkers may have potential for early detection of acute kidney injury.

AIM: The aim of the study was to test two urinary biomarkers: Kidney injury molecule-1(KIM-1) and liver-type fatty acid binding protein (L-FABP) as markers of kidney injury following coronary angiography.

METHODS: This is a prospective non-randomized controlled trial, performed in two large teaching hospitals. Patients were recruited from the catheter lab or form nephrology outpatient clinics. In group (A), 100 patients with AKI on top of CKD after coronary angiography and Group B: Thirty-one patients with stable CKD as a control. KIM-1 and L-FABP were measured at base line and after 3 months.

RESULTS: In group (A), 100 patients who had acute on top of CKD after coronary angiography, stage progression occurred in 15 patients in group (A) compared to two patients in group (B) (p = 0.28). The median change in eGFR after 3 months was not statistically significant between both groups (p = 0.8). Median baseline urinary liver-type fatty acid binding protein was higher in Group A compared to Group B (3.7 μg/g vs. 1.82μg/g). The change in L-FABP from baseline to 3 months was significant between both groups (p < 0.001). The median urinary concentrations of KIM-1 and L-FABP were higher at the end of the follow-up compared to base line values in both groups, (p < 0.000).

CONCLUSION: Urinary L-FABP correlates with kidney function decline in patients with acute on top of CKD after coronary angiography. Urinary levels of KIM-1 and L-FABP at 3 months increase significantly compared to baseline in patients with progressive CKD.

Introduction

There is a cross-talk between acute kidney injury (AKI) and chronic kidney disease (CKD). CKD constitutes a substantial risk factor for AKI development; an AKI episode may result in worsening of CKD stage [1], [2], [3], [4], [5], [6]. CKD is associated with increased risk of cardiovascular disease and mortality, proportional to glomerular filtration rate decline [7], [8], [9]. In hospital mortality due to the development of contrast-induced nephropathy (CIN) after coronary angiography has improved [10], [11], [12]. However, data regarding the long-term outcome is lacking. The effect of CIN on outcome may persist for up to 10 years [13].

A few biomarkers have shown variable sensitivity and specificity in early detection of CKD progression. CKD progression is classified using formulae to estimate glomerular filtration rate (eGFR) and measurement of proteinuria, both are easily available but limited by a number of fallacies [14].

Estimation of GFR reflects late functional changes; thus, eGFR is not considered an early marker of kidney damage. Plasma markers used in calculating eGFR (creatinine and urea) show significant increases only after about 50% of the GFR has been lost. In addition, these plasma markers are confounded by a large number of variables, including age, gender, race, muscle mass, muscle metabolism, hydration status, and medications. Furthermore, the enhanced tubular secretion of creatinine that is characteristically encountered at the lower rates of GFR results in an overestimation of renal function [15]. Recently, different plasma and urinary proteins have been evaluated as early biomarkers of CKD progression [15]. Each of these proteins has limitations that reduce reliability a as a sole biomarker of CKD progression. Kidney injury molecule (KIM-1) and liver-type fatty acid-binding protein (L-FABP) have shown a potential in a number of subclinical studies; this is much less the case with clinical studies on human participants [16], [17], [18], [19]. Our study aims to evaluate two urinary biomarkers in predicting CKD progression after coronary angiography. We used two biomarkers to enhance the prediction of progression.

Patients and Method

Study population

This study is a prospective observational study conducted in the Emergency department at two large teaching hospitals Kasr Al Ainy University Hospitals and Zagazig University Hospitals during the period from January 2016 to December 2017. Ethics and Research Committee of the National Research Centre approved this protocol. One hundred and thirty-one adults enrolled in this study in two groups. Patients in Group A were recruited from the catheter-lab after fulfilling the inclusion criteria for AKI after undergoing coronary angiography. Patients in Group B were recruited for nephrology clinics with different stages of CKD.

Group A (cases)

Hundred patients with different CKD stages, with diagnosis of AKI after coronary angiography were excluded from the study. Patients with end-stage kidney disease (ESKD) or receiving renal replacement therapy (RRT) at the time of recruitment (before coronary angiography), were excluded from the study. Patients were recruited while in hospital and were then followed up in the nephrology out-patients' clinic.

Diagnostic criteria for CKD: According to KDIGO definition of CKD, as either eGFR < 60 ml/kg/min/1.73 m^2 present for at least 3 months or the presence of kidney damage as denoted by structural or functional abnormalities other than decreased eGFR.

CKD stages were classified according to the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) [20], classified into:

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
- Stage 2: Mild reduction in eGFR (60–89 mL/min/1.73 m^2)
- Stage 3a: Moderate reduction in eGFR (45–59 mL/min/1.73 m^2)
- Stage 3b: Moderate reduction in eGFR (30–44 mL/min/1.73 m^2)
- Stage 4: Severe reduction in eGFR (15–29 mL/min/1.73 m^2)
- Stage 5: Kidney failure eGFR < 15 mL/min/1.73 m2 or dialysis)

AKI after coronary angiography was diagnosed based on RIFLE criteria (Table 1) as defined using the Risk, Injury, Failure, Loss, and End-stage Kidney Disease [21]. Baseline values were the last pre-angiogram values, while peak values were obtained within 7 days following the coronary angiogram.

Table 1: RIFLE criteria for the diagnosis of acute kidney injury

Stage	GFR[a] Criteria	UO[b] Criteria
Risk	SCrc increased 1.5-2 times baseline or GFR decreased >25%	UO < 0.5 mL/kg/h < 6 h
Injury	SCr increased 2–3 times baseline or GFR decreased >50%	UO < 0.5 mL/kg/h >12 h
Failure	SCr increased >3 times baseline or GFR decreased 75% or SCr ≥4 mg/dL; acute rise ≥0.5 mg/dL	UO < 0.3 mL/kg/h 24 h (oliguria) or anuria 12 h
Loss of function	Persistent acute renal failure: Complete loss of kidney function >4 wk (requiring dialysis)	Loss of function
ESRD[d]	Complete loss of kidney function >3 mo (requiring dialysis)	ESRD[d]

[a]GFR, glomerular filtration rate, [b]UO, urine output, [c]SCr, serum creatinine, [d]ESRD , end-stage renal disease

Group B (control): Thirty-one patients with different CKD stages with no episodes of AKI.

Informed consents had been obtained from all participants. Clinical assessment of participants included: Complete medical history and clinical examination including thorough cardiac examination. Estimated GFR, albumin creatinine ratio (ACR), urinary KIM-1, and L-FABP were measured at recruitment (baseline) and 3 months after angiography in Group A and as a base line and after 3 months in the control group. Comorbid conditions such as diabetes mellitus and hypertension were recorded. Type 2 diabetes was diagnosed using the criteria proposed by the American Diabetes Association. (ADA)

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Fasting and 2 h post-prandial glucose levels in venous blood were measured with an autoanalyzer (Automated Beckman analyzer Au 680). Hypertension was defined as mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, a diagnosis of hypertension, or current use of antihypertensive medications.

Eligibility criteria

Eligible patients were CKD patients admitted to hospital from January 2016 to December 2017 who developed AKI after coronary angiography. The control arm included patients with stable CKD, followed up in the nephrology clinic during same period without

clinically evident AKI. The four-variable Modification of Diet in Renal Disease (MDRD) Study equation was used to estimate eGFR in our patients. The level of albuminuria was defined by the National Kidney Foundation definition (Table 2).

Table 2: Albumin to creatinine ratio defined by National Kidney Foundation as

Category	ACR (mg/g)	Terms
A1	30	Mildly increased
A2	30–300	Moderately increased
A3	>300	Severely increased

Exclusion criteria

As per protocol, we excluded patients receiving renal replacement therapy (dialysis or transplantation); inability to give a consent is considered as exclusion criteria.

Coronary Angiography Study and Contrast Used

Coronary catheterizations were done using Philips (CV20, 2011-Netherland) and Siemens (Axiom Artis DFC 35875) with imaging speed 15 frame per second (fps). IOHEXOL (OMNIPAQUE)(General Electric Company) dye which is a nonionic, water-soluble radiographic contrast medium with a molecular weight of 821.14 (iodine content 46.36%) was used in our patients.

Plasma and urine sample collection

Blood samples were obtained from patients after obtaining formal consent. Blood samples were centrifuged to obtain the plasma samples. Urine samples were obtained to measure urinary KIM-1 and L-FABP levels.

Determination of urinary KIM-1 and L-FABP

KIM-1 was measured using microbead-based sandwich ELISA technique on Bioplex-200 platform (BioRad, Hercules, CA). L-FABP measured by two-step sandwich ELISA assay (CMIC, Tokyo, Japan).

Statistical analysis

Summary statistics were done. Numerical variables are presented as mean (SD) for normally distributed data and median (Minimum-Maximum) for non-normally distributed data. Categorical variables are presented as frequencies and percentages. Chi-squared test and Fischer's exact test were used to categorical variables. Numerical data were tested for normality by the by the Shapiro–Wilk normality test. Normally distributed data were analyzed using independent samples t-test. Data found to be non-normally distributed

were analyzed using the Mann–Whitney U-test. Paired samples were compared using the paired-samples t-test or the Wilcoxon signed-rank test as appropriate. Logistic regression analysis was performed to explore predictors of CKD stage progression. Predictors were tested for linearity before modeling. Data analysis was performed using Statistics/Data Analysis (STATA) version 13.1 software.

Results

Study population

The baseline characteristics of both groups are shown in Table 1. The proportion of females was higher than males in both groups, with no significant difference between groups. The prevalence of diabetes was significantly higher in CKD who developed AKI after coronary angiography (Group A), 51% versus 29% in control group (p = 0.03). In addition, they had significantly higher systolic and diastolic values (p < 0.0001) and had more frequent heart failure (P=0.01) and they were significantly older than Group B, (p = 0.0001) as shown in Table 1.

Baseline eGFR and ACR levels

Those who had coronary angiography had significantly lower mean pre-angiographic eGFR, KIM-1 concentration, and significantly higher ACR and mean L-FABP concentration than control group (P<0.05). CKD stages distribution showed that most of the patients had Stage 3A CKD in both groups. However, more prevalent earlier stage (Stage 2 CKD), P=0.01 with a milder degree of microalbuminuria, and P=0.0001 was found in control group (Table 3).

Table 3: Baseline patients characteristics

Characteristics	Cases n = 100	Control n = 31	p value
Age Mean (SD)	71.14 (5.57)	61.16 (6.42)	<0.0001
Gender			
Male/Female	35/65	12/19	0.7
DM (N/%)	51 (51%)	9 (29%)	0.03
HF (N/%)	47 (47%)	7 (22.6%)	0.01
Systolic BP	147.23 (13.77)	126.39 (9.79)	<0.0001
Diastolic BP	78.89 (9.59)	71.03 (9.46)	0.0001
Baseline CKD stage			
Stage_1_Mild_CKD (N/%)	0	0	
Stage_2_Mild_CKD (N/%)	10 (10%)	9 (29%)	0.01
Stage_3A_Moderate_CKD (N/%)	65 (65%)	13 (41.9%)	
Stage_3B_Moderate_CKD (N/%)	25 (25%)	8 (25.8%)	
Stage_4_Mild_CKD (N/%)	0	0	
Stage_5_End_Stage_CKD (N/%)	0	1 (3.2%)	
Baseline ACR (mg/g)			
< 30	9 (9%)	24 (77.4%)	<0.0001
30-300	91(91%)	7 (22.6%)	
>300	0	0	
eGFR Median (IQR)	48 (44–53)	54 (42.5–60.2)	0.02
ACR Median (IQR)	52 (46–60)	23.1 (19.4–28.8)	<0.0001
KIM ng/g Mean (SD)	629.83 (119.55)	807.22 (114.02)	<0.0001
L-FABP µg/g Median (IQR)	3.7 (3.14–4.15)	1.82 (1.72–1.85)	<0.0001

DM: diabetes mellitus; HF: Heart failure; BP: Blood pressure; CKD: Chronic kidney disease. ACR: Albumin creatinine ratio; eGFR: Estimated glomerular filtration rate; KIM-1: Kidney injury molecule-1; L-FABP: Liver-type fatty acid binding protein.

AKI stage in the 100 patients who underwent angiography

Most of them (71%) developed a mild degree of AKI (Stage 1) after coronary angiography, followed by 18% and 11% of severe and moderate AKI, respectively (Table 4).

Table 4: AKI classification according to RIFLE criteria in patients underwent coronary angiography

Stage	No	%
Stage 1 (Risk of RIFLE criteria)	71	71%
Stage 2 (Injury of RIFLE criteria)	11	11%
Stage 3 (Failure of RIFLE criteria)	18	18%

Changes of eGFR, ACR, KIM-1, and L-FABP from baseline to the end of follow-up (after 3 months)

Non-significant changes in mean eGFR occurred in both groups at the follow-up, (Table 3), with no significant difference in its delta change between groups (Table 5).

The median urinary concentrations of KIM-1 and L-FABP were increased significantly after 3 months follow-up compared to base line values in both groups ($p < 0.0001$). As regard their delta change comparison, the rise in KIM-1 was significantly higher in Group A (Table 5). In addition, CKD patients who had coronary angiography had a significant increase of ACR after 3 months, $p < 0.0001$ (Table 3). Delta change in ACR revealed a significant higher elevation in Group A compared to Group B ($p = 0.04$) (Table 6).

Factors associated with progression of CKD stage

Progression of CKD stage occurred in 15 patients from the Group 1 and only two patients from the control group (Group B). Logistic regression analysis of all the 130 patients revealed that higher systolic blood pressure as well as higher baseline eGFR are predictors of CKD stage progression, $p = 0.01$ (Table 7). Twenty-five patients experienced CKD stage regression after 3 months of follow-up. The remaining patients had stable CKD over 3 months.

Discussion

In our study, we assessed the baseline kidney function by eGFR. CKD severity is a very strong risk factor for AKI development after coronary angiography. Our study cohort included different age groups not only elderly like previous two studies: Newsome *et al* and Parikh *et al*. [2], [3]. Our study is prospective in contrast to different retrospective studies in this field [22]. The study was done on non-dialysis patients, which represent the majority of CKD patients, to give a complementary data to other studies focusing on dialysis-requiring patients [23], [24], [25], [26].

Effect of baseline proteinuria on the association between AKI and subsequent CKD progression was shown in our study and the most important issue in our study is using simple urine analysis with low cost for KIM-1 and L-FABP not a pathological examination like some studies [25], [27].

Reviewing literature, we found only one study addressing CKD progression after coronary angiography. They used serum creatinine and eGFR in determination of kidney function decline, which had several limitations [28]. In addition, it was a retrospective study; participants' selection was limited to patients who had pre- and post-angiography serum creatinine measurements including measurements within 7 days of coronary angiography as part of their clinical care. Second, episodes of AKI and their severity in that study may have been misclassified due to our dependence on existing creatinine measurements captured following coronary angiography [28].

Patients who developed AKI were older, with several comorbidities including diabetes mellitus, a higher degree hypertension, with a higher prevalence of heart failure, all are well known risk factors for cardiovascular diseases which may necessitate coronary angiography as proved in many studies [29], [30]. In our study, CKD patients who developed AKI had a significantly lower pre-angiographic eGFR, a higher ACR and more advanced CKD stages at the baseline, as well a significant increase of ACR during subsequent measurement after 3 months of follow-up. However, more progression in CKD stage occurred in Group A (acute on top of chronic kidney disease) compared to only two patients in the Group B (control group). In the literature, reduced eGFR and increased proteinuria were found to be associated with risk of cardiovascular events, and death [7], [8], [9].

The pathophysiological relationship between CKD and AKI is complex and yet to be fully elucidated [31]. Progression of CKD after AKI episode could be explained by that, AKI on top of CKD causing

Table 5: The change in Kidney functions and renal injury markers in cases versus control

Parameters	Cases			Control		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
eGFR Median (IQR)	48 (44–53)	50 (45–52)	0.1	54 (42.5–60.2)	55.5 (45.5-60.2)	0.45
ACR Median (IQR)	52 (46–60)	68 (58–76)	<0.0001	23.1 (19.4-28.8)	26.6 (20.5-32.2)	0.1
KIM Mean (SD)	629.83 (119.55)	677.84 (123.81)	<0.0001	807.22 (114.02)	837.61 (103.48)	**<0.0001**
L-FABP Median (IQR)	3.7 (3.14–4.15)	3.97 (3.27–4.53)	<0.001	1.82 (1.72-1.85)	1.9 (1.85-1.94)	**<0.001**

ACR: Albumin creatinine ratio, eGFR: Estimated glomerular filtration rate. KIM-1: Kidney injury molecule-1, L-FABP: Liver-type fatty acid binding protein.

pathologic growth arrest in the proliferating tubules, failure to re-differentiate, and finally become atrophic. These abnormal tubules exhibit persistent, unregulated, and progressively increasing pro-fibrotic signaling along multiple pathways [32].

Table 6: Delta change in injury markers in cases versus control

Parameters	Cases	Control	p value
Δ change in KIM	46 (35–56)	44 (40–47)	0.04
Δ change in LFABP	0.27 (0.12–0.35)	0.11 (0.08–0.13)	<0.001
Δ change in eGFR	2 (-3–4)	1.7 (−2.4–3.4)	0.8
Δ change in ACR	15 (9–21)	4.4 (−5.4–9.7)	<0.0001

ACR: Albumin creatinine ratio, eGFR: Estimated glomerular filtration rate, KIM-1: Kidney injury molecule-1, L-FABP: Liver-type fatty acid binding protein.

A mild non-significant increase in mean eGFR in both groups comes in agreement with study by Garg *et al*. concluded that an intervention that reduced the risk of mild to moderate acute kidney injury did not alter longer-term kidney function at 1 year [33].

Table 7: Predictors of CKD progression

Predictors	OR (95% Conf. Interval)	p value
Age	1.3 (0.93–1.47)	0.9
Gender		
Female	0.45 (0.16–1.26)	0.1
DM	2.39 (0.83–6.29)	0.1
CVD	2.24 (0.79–6.32)	0.1
Systolic BP	1.05 (1.01–1.09)	0.01
Diastolic BP	1.03 (0.97–1.08)	0.3
Baseline eGFR	1.08 (1.01–1.16)	0.01
Baseline ACR	1.01 (0.98–1.04)	0.6
Baseline KIM-1	0.99 (0.99–1.002)	0.4
Baseline L-FABP	1.3 (0.56–1.51)	0.3

DM: Diabetes mellitus, CVD: Cardiovascular disease, BP: Blood pressure; ACR: Albumin creatinine ratio, eGFR: Estimated glomerular filtration rate, KIM-1: Kidney injury molecule-1, L-FABP: Liver-type fatty acid binding protein.

In our study, patients who developed AKI had a significant lower mean KIM-1 and a significant higher mean L-FABP concentration at the baseline measurements compared to control group. These values are significantly increased by time at the end of the follow-up in both cases who developed AKI and in control group. The delta change in KIM-1 and ACR and L-FABP was significantly higher in cases than the control group. In either cases of CKD stage progression or regression, kidney injury biomarkers and ACR were significantly increased after 3 months. However, when we compare delta change of these biomarkers, we found non-significant results in relation to CKD stage progression. Some studies found that L-FABP correlated with degree of CKD progression [34], [35], while others found no significant correlation [36]. The reason for this discrepancy may be explained by the transient rise of L-FABP following renal injury. One study found that L-FABP best correlated with kidney injury as early as 4 h post-coronary angiography [37]. This denotes that the rise in L-FABP is transient.

Higher values of biomarkers in the control group may indicate possible early renal damage in the absence of persistent albuminuria and potential capabilities of urinary KIM-1 and L-FABP in early detection of renal injury among them. In a large health screening study, urinary excretion of L-FABP was found to be increased in subjects with hypertension and diabetes mellitus, even in the absence of overt kidney damage [18]. These comorbidities are also found in the control group.

Joseph Bonventre found that, KIM-1 promotes the scar tissue formation in chronic kidney disease and the kidney cells that produce it, maintains its expression over time in chronic kidney disease but this observation was unfortunately, found in mice [19]. A study found that, KIM-1 staining in the kidney biopsy of CKD patients with different etiology, correlated positively with morphological damage and negatively with renal function. Urinary KIM-1 levels measured in a subset of these patients were also negatively correlated with eGFR (r = -0.37; p = 0.016) [27].

In the literature, L-FABP levels were significantly higher in the group of patients with mild CKD who progressed to more severe disease in non-diabetic CKD patients [15]. In another small study of patients with type-2 diabetes, urinary L-FABP levels were associated with degree of proteinuria[17]. These studies are consistent with our findings.

Limitations of our study

This study has a number of limitations. First, we did not address the relation to mortality, to the effect of repeated AKI episodes and short time of follow-up. Second, there is a potential selection bias since the study is none randomized. There is a discrepancy between the numbers of cases to controls.

Strength of the study

This is a prospective study testing two novel urinary biomarkers using a simple urine sample.

Conclusion

Urinary L-FABP correlates with kidney function decline in patients with acute on top of CKD after coronary angiography at baseline compared to patients with stable CKD. Urinary level of KIM-1 and L-FABP at 3 months increases significantly compared to baseline in patients with either stable or progressive CKD. The change in urinary L-FABP was more significant in patients with CKD progression.

Compliance with Ethical Guidance

All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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