Significance of Liver Fatty Acid Binding Protein after Coronary Angiography for Early detection of Acute Kidney Injury in Diabetics with normal Renal Angiography

Yasser Abdelgaleel Omar

Department of Cardiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Abstract: Background: Contrast-induced acute kidney injury (CI-AKI) is a complex syndrome of acute renal failure occurring after the administration of iodinated contrast media. Patients with diabetes mellitus often require coronary angiography and coronary intervention and are at risk of CI-AKI. The small changes in serum creatinine (SCr) may be associated with poor outcomes and severe AKI so the performance of urinary L-FABP which is a 14-kDa protein expressed in proximal tubular epithelial cells as an early detection marker of CI-AKI has shown promise in various clinical settings. We tested the hypothesis whether L-FABP could represent an early biomarker of CIN in diabetic patients with normal serum creatinine undergoing cardiac catheterization in comparison with non-diabetic patients. **Objective:** The aim of this study is to prospectively assess specificity and sensitivity of L-FABP as a renal biomarker for quick detection of contrast induced nephropathy in diabetic and non-diabetic patients scheduled for coronary angiography. **Methods:** The present study was conducted on 84 patients admitted to Al-Taiseir international hospital with coronary artery disease and subjected to coronary angiography in cardiac catheterization unit. Patients classified into two groups diabetic and non-diabetic and then sub classified according to the RIFLE criteria on a day-to-day basis according to their worst creatinine and/or lowest urine output. Risk factors were evaluated for CIN, including: Patients with diabetes mellitus, hypertensions, dyslipidemia and ischemic heart disease. The L-FABP was studied for early prediction of acute kidney injury before and after coronary angiography. **Results:** After coronary angiography mean serum creatinine was increased (p value < 0.006). The mean creatinine clearance was reduced in our patients after usage of contrast (p value < 0.000). Mean L-FABP significantly increased 4 hours after coronary angiography and the sensitivity of L-FABP to CIN is 86% while specificity is 93% (with an AUC-ROC of 0.95) without significant difference in diabetic and non-diabetic groups. **Conclusion:** This study showed the importance of urinary L-FABP levels in quick detection of AKI associated with contrast administration earlier than serum creatinine after coronary angiography with similar prevalence of CIN in diabetic and non-diabetic patients. The sensitivity of L-FABP to CIN is 86% and specificity is 93%.

[Yasser Abdelgaleel Omar. **Significance of Liver Fatty Acid Binding Protein after Coronary Angiography for Early detection of Acute Kidney Injury in Diabetics with normal Renal Angiography.** *J Am Sci* 2016;12(9):116-122]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 18. doi:10.7537/marsjas120916.18.

Key words: Acute kidney injury, L-FABP, CIN, Coronary angiography.

1. Introduction

Diabetes is the most important contributor to the growing burden of ESRD, and patients with diabetes are also at a greater risk of requiring hospitalizations and experiencing acute kidney injury (AKI). Two studies of type 1 diabetes and three studies of type 2 diabetes address the clinical significance of urinary liver-type fatty acid-binding protein in patients with diabetic nephropathy. [1-5] AKI is one of a number of conditions that affect kidney structure and function. [6] Contrast-induced nephropathy (CIN), subtype of AKI, is a complex syndrome of acute renal failure occurring after the administration of iodinated contrast media, has recognized as a serious complication of percutaneous coronary intervention (PCI) and may cause increased morbidity and mortality. [7]

At present, serum creatinine, which is used to measure the glomerular filtration rate (GFR), is the most commonly used marker of renal function. Unfortunately, serum creatinine is a delayed and unreliable indicator of AKI as it is influenced by multiple non-renal factors, such as muscle mass, can take several hours or days to reach a new steady state, the serum creatinine level may not rise until more than half of the kidney function has been lost and does not allow differentiation between hemodynamically mediated changes in renal function, such as pre-renal azotemia from intrinsic renal failure or obstructive uropathy. Given the limitations of serum creatinine as a marker of renal function, different urinary and serum proteins; molecules; and, most recently, micro RNAs have been rigorously investigated over the past decade as possible biomarkers for early and accurate identification of AKI. [8]

Liver-type fatty acid binding protein (L-FABP), one such candidate biomarker, is a 14-kDa protein expressed in proximal tubular epithelial cells. The L-FABP gene is responsive to hypoxic stress, which occurs in the setting of kidney ischemic reperfusion injury. As a consequence, urinary excretion of L-

FABP reflects the stress of proximal tubular epithelial cells, correlating with the severity of ischemic tubular injury. The performance of urinary L-FABP as an early detection marker of AKI has shown promise in various clinical settings. [9]Although studies in which the advantages of urinary L-FABP compared to the existing clinical markers have been few, the clinical relevance of urinary L-FABP as a predictor of progression of DN, of requirement for dialysis or cardiovascular events and of anemia, or as a target for therapeutic regimens.[10] This study was designed to assess the L-FABP as renal biomarker in quick detection of CI-AKI after coronary angiography in diabetic and non-diabetic group.

Since treatment of CI-AKI after it has occurred is ineffective, efforts to prevent or attenuate the injury are the focus of ongoing early diagnosis and careful long-term treatment of patients with type 2 diabetes mellitus and coronary artery disease. Ideal goals for vascular risk factor modification include blood pressure of 130/80mmHg or better, LDL cholesterol less than 70 mg/dL and hemoglobin A1C less than 7%.

2. Patients and methods:

All data were collected in the context of our current practice, and every patient or next of kin was informed that collected data could be used for research purpose. Our institutional review board approved this non-interventional study and waved the need for informed consent. The study was conducted on 84 patients admitted to the Al-Taiseir international hospital with coronary artery disease and scheduled to coronary angiography in cardiac catheterization unit. Patients classified into two groups diabetic and non-diabetic and then sub classified according to the RIFLE criteria on a day-to-day basis according to their worst creatinine and/or lowest urine output. Patients with history of AKI defined by RIFLE criteria, chronic renal impairment, prior kidney transplant, end-stage kidney disease, renal replacement therapy (RRT) prior to admission, obstructive etiology for AKI, all types of shocks, and all types of cardiomyopathies were excluded.

All candidate patients were subjected to complete history taking including demographic data, medical history of chronic illness and previous drug history. Clinical assessment for the patients was done including vital signs. Laboratory investigations in the form of CBC, liver function, kidney functions and serum electrolytes were done on admission. Electrocardiography (ECG) and Echocardiography (ECHO) and abdominal ultrasounds (US) were done on admission.

Urine samples were collected from each patient on admission and four hours after coronary angiography. L-FABP measurement was performed by the Enzyme linked immunosorbent assay (ELISA) method, in the biochemistry laboratory of Al-Taiseir international hospital. Measurement was performed directly on urine samples.

In addition to demographic data and weight, the following data were collected mean arterial pressure (MAP), ECHO data, SCr level, estimated creatinine clearance, type and dose of contrast agent. Different risk factors for acute kidney injury were evaluated, including: diabetes, hypertension, dyslipidemia, smoking and amount of dye used.

Renal function was assessed by RIFLE criteria, baseline creatinine was measured and a low normal value for baseline GFR (75 mL/min per1.73 m2) was assumed, as recommended by the Acute Dialysis Quality Initiative [11]. Renal angiography was done in association of coronary angiography.

3. Results:

Eighty four patients scheduled for coronary angiography were included in the study. The patients' characteristics upon enrolment are shown in Table-1. There were no differences in demographic characteristics among the studied patients. Patients in our study had mean LVESD of 4.34±4.41 in CIN group and 3.42± 0.46 in non CIN group. Mean LVEDD of 5.24 ±0.60 in CIN group and 5.14± 0.52 in non CIN group. Finally mean EF%63.53± 6.12 in CIN group and 63.85±5.93 in non CIN group.

Table (1): Age and ECHO parameters of studied patients

	CIN	Value	SD
Age	Y	58.09	± 7.68
	N	56.20	± 6.89
LVESD	Y	4.43	±4.41
	N	3.42	±0.46
LVEDD	Y	5.24	± 0.60
	N	5.14	± 0.52
EF%	Y	63.53	± 6.12
	N	63.85	±5.93

Mean serum creatinine level in our patients studied was 0.9± 0.142and was increased after coronary angiography1.02±0.19 (P value 0.000) as shown in table 2 and figure 1 but still not beyond the critical value. Also the mean creatinine clearance was decreased after use of contrast agent during coronary angiography (128.94± 25.17) versus 94.02±24.03) P value < 0.000. **As well as mean urine L-FABP was significantly increased after use of contrast agent during angiography p value < 0.000 as shown in table 2 and figure 2.**

Table (2): S. creatinine, creatinine clearance and L-FABP data of studied patients

	Mean		Student test	
			T	P
S. Creatinine	Before angiography	0.9± 0.142	-8.080	0.006
	After angiography	1.02±0.19		
Creatinine clearance	Before angiography	128.94± 25.17	9.855	0.000
	After angiography	94.02±24.03		
L-FABP	Before angiography	5.19± 1.94	-11.953	0.000
	After angiography	22.47±13.63		

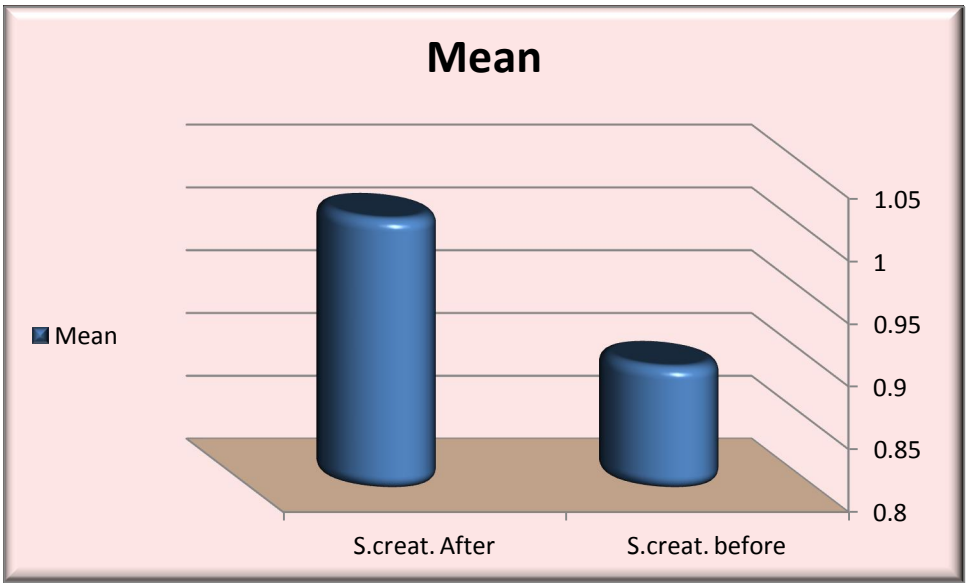

Figure 1: S. creatinine in the studied patients

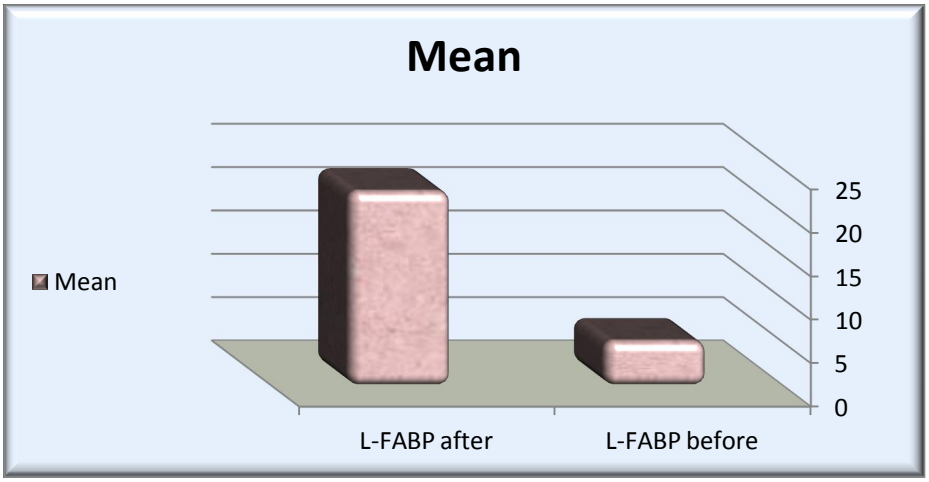

Figure 2: L-FABP in the studied patients

In our study, we found a similar prevalence of CIN in diabetic patients over non-diabetic patients with normal serum creatinine (54.2% vs. 47.2%). These results indicated that urinary L-FABP accurately a suitable biomarker for early detection of CI-AKI. As we select our diabetic group that had no evident progressive nephropathy there was no statistically significance between L-FABP in both groups. Show table 3 and figure 3.

Hypertension, dyslipidemia and smoking as a risk factors for AKI and my increase risk incidence of CI-AKI was not significantly related to documented CIN in our study as in table 3.

Table-3: CI-AKI groups and DM, HTN, IHD, Dyslipidemia and smoking.

L-FABP vs Risk factors		CIN		Chi-Square Tests (sig.)
		Yes	No	
DM	Yes	**54.2%**	45.8%	0.493
	No	**47.2%**	52.7%	
IHD	Yes	**58.3%**	41.7%	0.053
	No	**33.3%**	66.7%	
HTN	Yes	58.7%	41.3%	0.188
	No	42.1%	57.9%	
Dyslipidemia	Yes	50.0%	50.0%	1.000
	No	51.8%	48.2%	

Ischemic heart disease was the main chronic associated condition in our study and there was significant difference between groups **p value 0.053**. Show table 3 and figure 4.

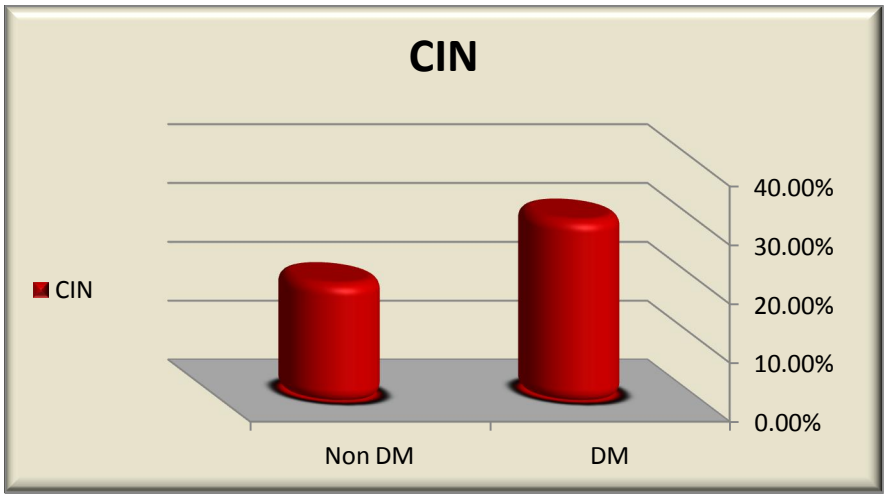

Figure 3: CIN in the DM and non DM groups.

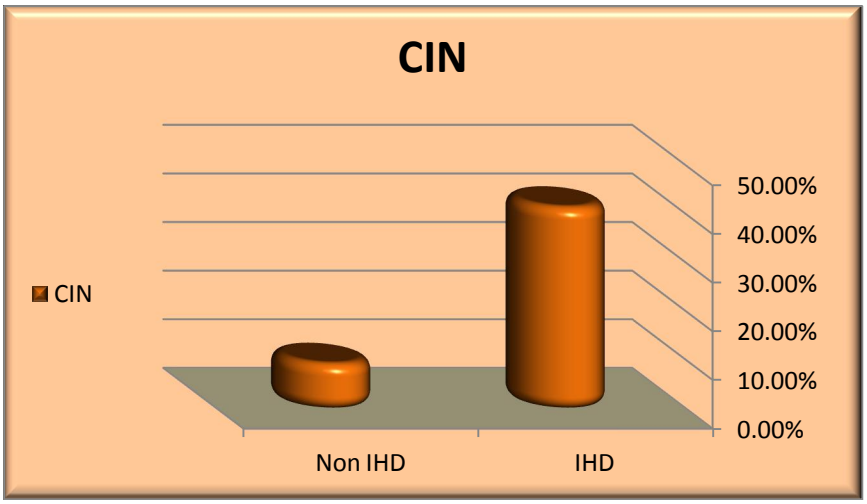

Figure 4: CIN in the IHD and non IHD groups.

The ROC curve was studied L-FABP level in relation to the decrease of creatinine clearance 4 hours after coronary angiography and found that specificity of 92% and sensitivity of 86% for AKI at 19.75 ng/ml of L-FABP value show figure 5.

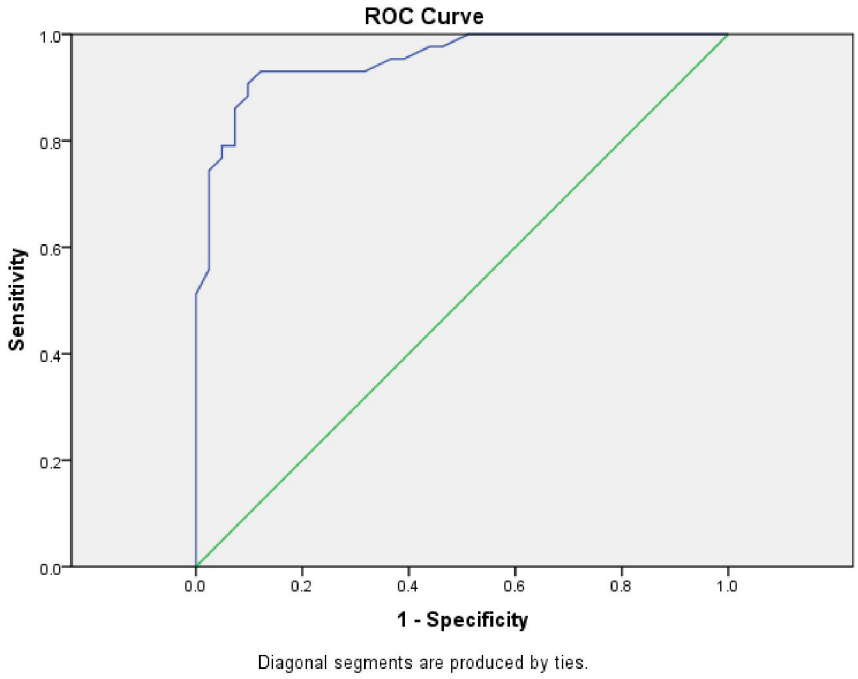

Figure 5: ROC curve study.

4. Discussion:

The sensitivity of L-FABP to CIN is 86% and specificity is 93% (with an AUC-ROC of 0.95). Urinary L-FABP sensitively and rapidly reflected contrast induced renal injury compared with creatinine in diabetics and non-diabetic's patients after contrast medium use. This implies that urinary L-FABP is more useful marker for the early detection of kidney injury than creatinine.

In the present study, we aim to prospectively assess specificity and sensitivity of L-FABP as a renal biomarker for early prediction of contrast induced nephropathy in diabetic and non-diabetic patients scheduled for coronary angiography.

Chronic associated conditions and risk factors in the studied patients were 46 patients (54.8 %) with hypertension, 60 patients (71.4 %) with ischemic heart disease, 28 patients (33.3 %) with dyslipidemia and 34 patients (40.5 %) smoker. There was no statistically significant difference of the studied patients except for ischemic heart disease. ***Yusuke Fukuda et al.,*** [12] had the first report that measurement of urinary L-FABP can be beneficial for the diagnosis of CI-AKI in acute coronary syndrome. Their study included 27 consecutive patients with stable angina (SAP group) or acute coronary syndrome (ACS group) who had undergone successful percutaneous coronary intervention (PCI), and controls (C group) enrolled 12 patients. Urinary and serum parameters were measured immediately before and after and 1 day after PCI, they found that the ratio of urinary L-FABP to urinary creatinine in the acute coronary syndrome group was significantly higher than those in both the Stable Angina and Control groups. Although our scheduled patients were elective and didn't have acute coronary syndrome but our results matched with ***Yusuke Fukuda***. Our results also matched with ***Rie Matsumori et al.,*** [13] study who demonstrated that urinary L-FABP levels in patients with acute myocardial injury, but not in patients with unstable angina, were significantly higher than those in the control group. However the difference in urinary L-FABP between AMI and UAP groups reported by Fukuda had not been elucidated because they didn't discriminate between AMI and UA.

When contrast nephropathy was defined by RIFLE criteria as an increase in serum creatinine by >25% of the baseline level after cardiac catheterization, the prevalence of CIN was 47.2% in non-diabetics and 54.2% in diabetics. In both groups we found a significant rise of urinary L-FABP four hours after coronary angiography. These results matched with ***Hiromasa Katoh et al.,*** [14] who demonstrated higher levels of urinary and serum markers such as L-FABP, NAG, Cys C, and b2- MG at baseline in patients who developed CI-AKI than in those without CI-AKI. The urinary L-FABP level at the baseline was the only independent predictor marker of CI-AKI after multivariate regression analysis when its cutoff value was 19.0 ng/ml. As the tubule-interstitial damage is the main pathological mechanism of CI-AKI. ***Yokoyama et al.*** [15] evaluated

the dynamics of renal L-FABP and the change in urinary L-FABP in the variety of tubule-interstitial damage in the FA-induced nephropathy model. They reported that the amount of renal expression and urinary excretion of L-FABP were significantly correlated with the severity of tubule-interstitial damage in human L-FABP transgenic mice. ***Eunjung Cho, et al.*** [16] suggested that urinary L-FABP could be an adjunctive and independent biomarker for detection of AKI as well as the prediction of prognosis in heterogeneous ICU patients. ***Malyszko J et al.,*** [17] found a significant rise in serum NGAL after 2, 4, and 8 hours, and in urinary NGAL and IL-18 after 4, 8, and 24 hours after cardiac catheterization. Serum cystatin C increased significantly 8 hours, reaching peak 24 hours after cardiac catheterization in both groups (diabetic and non-diabetic patients), and then decreased after 48 hours while L-FABP and KIM-1 increase significantly after 24 and 48 hours after cardiac catheterization.

The increased risk of CIN in diabetic patients with reduced renal function is well documented [18]. Yet, diabetic patients without overt renal dysfunction are also at risk as compromised renal function may not manifest until an acute renal insult results from the administration of contrast medium. This refers to inadequate compensatory vasodilator responses. It is known that tubule-interstitial damage plays an important role in diabetic nephropathy [19]. Therefore, it would potentially be beneficial if albuminuria, as a marker of glomerular damage, could be supplemented by a marker of tubular damage to provide a more complete status of the kidney injury. ***Kamijo et al.*** [20] reported that u-LFABP predicts a decrease in estimated glomerular filtration rate in type 2 diabetic patients with diabetic nephropathy. This finding supports our results as our selected patient didn't have diabetic nephropathy and indicates that u-LFABP is a promising marker in acute kidney injury in diabetic and non-diabetic patients. ***Malyszko J et al.,*** [17] tested the hypothesis whether L-FABP and other biomarkers could represent an early biomarker of contrast nephropathy (CIN) in diabetic patients with normal serum creatinine undergoing cardiac catheterization in comparison with non-diabetic patients. They conclude that CIN was similarly prevalent in both diabetic and non-diabetic patients undergoing cardiac catheterization. Our results not matched with ***Nielsen SE et al.,*** [3] who reported that urinary u-LFABP is increased in diabetic patients, even before they develop signs of glomerular damage, micro-albuminuria or macro-albuminuria. This indicates that tubular damage is present at an early stage of diabetic kidney damage, even before the development of micro-albuminuria.

Our findings may have important implications for the clinical management of patients undergoing cardiac catheterization. The "window of opportunity" is narrow in contrast nephropathy, and time is limited to introduce proper treatment after initiating insult, particularly when patients are discharged within 24 hours after the procedure. So development in renal biomarkers has led to concepts like 'subclinical AKI' and 'renal angina 'which are biomarker-guided and describe the clinical condition characterized by positive biomarker and negative creatinine findings. [21] In a patient with multiple AKI risk factors, one would need a smaller change in SCr and urine output to raise clinical suspicion for evolving AKI (analogous to the diabetic man with heartburn). However, in another patient with fewer risk factors, it would take a bigger change in SCr to reach that same level of suspicion.

The strength of our study is its prospective design, simultaneous measurement of urinary L-FABP on low-risk population. The main limitation is that this is a single-center study and we didn't measure urinary L-FABP level during a further follow up period as patients were discharged early. Urinary assay requires only 150 ml of urine, and results are available within few minutes. It could be particularly useful in patients with impaired kidney function, a population particularly prone to rapid deterioration of renal function.

Conclusions:

Coronary artery disease is a major complication of diabetes mellitus. Thus, patients with diabetes mellitus often require coronary angiography and coronary intervention and are at risk of CIN. It is evidently crucial to establish noninvasive and easily applicable methods to monitor the risk of AKI development such as L-FABP biomarker.

We concluded that the specificity for CI-AKI 93% and sensitivity of 86% at 19.75 ng/ml of L-FABP value and prevalence of CI-AKI was 47.2% in non-diabetics and 54.2% in diabetics.

References:

1. Kamijo-Ikemori A, Sugaya T, Yasuda T, et al. Clinical significance of urinary liver-type fatty acid-binding protein in diabetic nephropathy of type 2 diabetic patients. Diabetes Care 2011; 34:691–6.
2. Nakamura T, Sugaya T, Kawagoe Y, et al. Effect of pitavastatin on urinary liver-type fatty acid-binding protein levels in patients with early diabetic nephropathy. Diabetes Care 2005; 28:2728–32.
3. Nielsen SE, Sugaya T, Tarnow L, et al. Tubular and glomerular injury in diabetes and the impact of ACE inhibition. Diabetes Care 2009; 32:1684–8.
4. Panduru N, Forsblom C, Saraheimo M, et al. Urinary Liver-type fatty acid-binding protein and

progression of diabetic nephropathy in type 1 diabetes. Diabetes Care 2013 [in press].
5. Suzuki K, Babazono T, Murata H, Iwamoto Y. Clinical significance of urinary liver-type fatty acid-binding protein in patients with diabetic nephropathy. Diabetes Care 2005;28:2038–9.2. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10: R73.
6. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34: 1913–1917.
7. Sait Demirkol, I Sevket Balta, I Emin Ozgur Akgul, et al. Hyperuricemia may be related to contrast-induce nephropathy after percutaneous coronary intervention. DOI: 10.6061/clinics/2013 (07)28.
8. Mishra J, Mori K, Ma Q, et al. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol. Dec 2004; 15(12):3073-82.
9. Paweena Susantitaphong, Monchai Siribamrungwong, Kent Doi, et al. Performance of Urinary Liver-Type Fatty Acid–Binding Protein in Acute Kidney Injury: A Meta-analysis. Am J Kidney Dis 2012; 61(3):430-439.
10. Atsuko Kamijo-Ikemori, Takeshi Sugaya, Daisuke Ichikawa. Urinary liver type fatty acid binding protein in diabetic nephropathy. Clinica Chimica Acta 424 (2013) 104–108.
11. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure V definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8(4): R204YR212, 2004.
12. Yusuke Fukuda, Shin-ichiro Miura, Bo Zhang et al, Significance of urinary liver fatty acid binding protein in cardiac catheterization in patients with coronary artery disease. Intern Med 2009 1; 48(19):1731-7.
13. Rie Matsumori, Kazunori Shimada, Takashi Kiyanagi et al, Clinical significance of the measurements of urinary liver-type fatty acid binding protein levels in patients with acute coronary syndrome. Journal of Cardiology 60 (2012) 168–173.
14. Hiromasa Katoh, Tsuyoshi Nozue, Yuya Kimura, et al. Elevation of urinary liver-type fatty acid-binding protein as predicting factor for occurrence of contrast-induced acute kidney injury and its reduction by hemodiafiltration with blood suction from right atrium. Springer Japan 2013; DOI 10.1007/s00380-013-0347-9.
15. Yokoyama T, Kamijo-Ikemori A, Sugaya T, Hoshino S, Yasuda T, Kimura K. Urinary excretion of liver type fatty acid binding protein accurately reflects the degree of tubulointerstitial damage. Am J Pathol 2009; 174: 2096-106.
16. Eunjung Cho, Ha Na Yang, Sang-Kyung Jo Won-Yong Choand Hyoung-Kyu Kim. The Role of Urinary Liver-Type Fatty Acid-Binding Protein in Critically Ill Patients. J Korean Med Sci 2013; 28: 100-105.
17. Malyszko J, Bachorzewska-Gajewska H, Poniatowski B, Malyszko JS, Dobrzycki S (2009) Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and normal serum creatinine. Ren Fail 31:910–919.
18. Parfrey, P. S., S. M. Griffiths, B. J. Barrett, M. D. Paul, M. Genge, J. Withers, N. Farid, & P. J. McManamon. (1989). Contrast material-induced renal failure in patients withdiabetes mellitus, renal insufficiency, or both. A prospective controlled study. *New England Journal of Medicine* 320 (3): pp. 143-149, ISSN 0028-4793.
19. Parving H-H, Østerby R, Ritz E. Diabetic nephropathy. In *The Kidney*. 6th ed. Brenner BM, Ed. Philadelphia, WB Saunders, 2000, p. 1731–1773.
20. Kamijo A, Sugaya T, Tanaka Y, Yasuda T, Kimura K. Urinary excretion of liver-typefatty acid binding protein (L-FABP) as auseful predictor of future renal in dysfunctionin type 2 diabetic nephropathy. Abstract Presented at Renal Week 27Oct–1 Nov 2009, San Diego, CA20. Nielsen SE, Sugaya T, Tarnow L, Lajer M, Schjoedt KJ, Astrup AS, Baba T, Parving HH, Rossing P. Tubular and glomerular injury indiabetes and the impact of ACE inhibition. Diabetes Care 2009; 32:1684–1688.
21. Goldstein SL, Chawla LS (2010) renal angina. Clin. J Am Soc Nephrol 5:943–949.

9/25/2016