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Original Article

Diagnostic Accuracy of L-FABP-to-Creatinine Ratio (LCR) for Prediction of Kidney Damage in Type-2 DM Patients Taking Albumin-to-Creatinine Ratio (ACR) as Gold Standard

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Abstract

Objective: To determine the diagnostic accuracy of LCR for the prediction of kidney damage in Type-2 Diabetes Mellitus patients keeping ACR as gold standard.

Methods: It was a descriptive study conducted in diabetic center of Lahore General Hospital on 70 Type 2 diabetics, 35 to 55 years old having negative spot urine dipstick test for albumin. After informed consent, urine samples were collected for measurements of ACR and LCR. Patients with cardiovascular disease, hypertension, liver disease, pregnancy, anemia or any other chronic disease were excluded. ACR 30-300 mg/g was labeled as having Diabetic Nephropathy (DN). Data was analyzed in SPSS-27.

Results: The mean ± SD age, BMI, duration of DM of participants was 49.6 ± 4.7 years, 29.3 ± 3.0 kg/m2, 6.2 ± 1 years respectively. Using 5.5 µg/g cut off value for LCR, the sensitivity, specificity, positive predictive value, negative predictive value, Youden's index and overall diagnostic accuracy was 85.5%, 93.3%, 0.98, 0.6, 0.78 and 0.87 respectively. Area under curve (AUC) was 0.81.

Conclusion: L-FABP has overall good diagnostic accuracy to predict kidney damage in Type-2 diabetics.

Keywords: Albumin, Creatinine, Liver type Fatty Acid Binding Protein, Creatinine, Type 2 DM, Kidney damage.

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Introduction

Diabetic nephropathy (DN) is one of the common microvascular complications of Diabetes Mellitus (DM). It affects 30-40 % of T2DM patients and has become a primary cause of chronic kidney disease (CKD) leading to end stage renal disease (ESRD). Being asymptomatic in the early course of the disease, results in difficulty to reverse the renal damage once nephropathy is established.[1-3]

Microalbuminuria is considered as an important glomerular biomarker of DN and estimation of albumin-to-creatinine ratio (ACR) is being utilized for detection of early kidney damage. However, the use of microalbuminuria to detect early kidney damage is limited since it does not capture damage to other sites of nephrons because quite a number of patients with persistent microalbuminuria still develop CKD without going through the phase of macro-albuminuria4. About 10-30% of patients with T2DM have deteriorated renal function even before the stage of microalbuminuria named as non-proteinuric diabetic nephropathy (NP-DN). This raises the question of diagnostic accuracy of ACR for early detection of renal damage.[5-7]

In addition to the glomerular damage, tubular interstitial damage also plays an important role in DN. Among various tubular biomarkers, liver-type fatty acid binding protein (L-FABP) is under investigation to be a potential biomarker for early diagnosis of kidney injury.[8] It is an

endogenous, intra-cellular protein present in the cytoplasm of renal tubular epithelial cells and hepatocytes to participate in fatty acid metabolism. There is increased production and excretion of L-FABP in urine in tubular injury due to hypoxia and oxidative stress.[9-12]

In this background this study was planned to determine the diagnostic accuracy of L-FABP-to- creatinine (LCR) in Type-2 diabetics to be used as a substitute of ACR or an adjuvant biomarker for the prediction of kidney damage.

Methods

It was a descriptive study conducted in the Diabetes center of Lahore General Hospital and Chemical Pathology Department of PGMI after approval from Advanced Studies and Research Board (ASRB) of University of Health Sciences (UHS). After informed consent, 70 patients of Type-2 DM, 35 to 55 years old having negative spot urine dipstick test for albumin were enrolled in the study. Patients with cardiovascular disease, hypertension, liver disease, pregnancy, anemia or any other chronic disease were excluded. The demographic and clinical data of participants were recorded in the predefined proforma.

After informed consent, urine samples were collected for measurements of ACR and LCR. The samples were centrifuged for 5 minutes at 3000 revolutions per minute to remove cellular components. Urinary creatinine and microalbumin was performed on the same day on automated Chemistry Analyzer Selectra Pro XL using photometric and turbidimetric Immunoassay respectively. The remaining supernatant was then aliquoted into labeled Eppendorf and stored at –80°C for the estimation of L-FABP on semi- automated ELISA Analyzer (Model: Stat Fax 2100). ACR (mg/g) and LCR (µg/g) was calculated by dividing microalbumin (mg) and L-FABP(µg) by creatinine (g) respectively. Data was analyzed in SPSS-27. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), Youden's index and overall diagnostic accuracy (DA) of LCR was calculated by appropriate formulae. Receiver Operator curve (ROC) was plotted to determine AUC for LCR.

Results

Out of 70 patients, 55 and 15 were labeled as DN and non-DN respectively on the basis of ACR as shown in Table 1. The demographic and clinical data of participants is shown in Table 1. The age, BMI, M:F were not statistically different between patients with and without DN but the duration of DM, HbA1c levels and LCR were significantly different between groups.

Using 5.5 µg/g cut off value for LCR, Sn, Sp, PPV, NPV, Youden's index and overall diagnostic accuracy calculated using 2×2 contingency table was 85.5%, 93.3%, 0.98, 0.6, 0.78 and 0.87 respectively as shown in Table 2. The AUC for LCR was 0.81 at 95% confidence interval to diagnose nephropathy (Figure 1).

Table 1: *Demographic and Clinical characteristics of study subjects.*

Variables	DN (n= 55)	Non DN (n=15)	p -value
(M : F)%	34 : 66	39 : 61	0.572
Age(years)	49.6 ± 4.7	48.3 ± 6.1	0.431
BMI (kg/m^2)	29.3 ± 3.0	28.3 ± 2.0	0.521
*Duration of DM (years)	6.2 ± 1	4.9 ± 1.4	*0.023
*HbA1c %	6.6 ± 0.5	8.1± 1.6	* 0.002
*LCR (µg/gCr)	4.8 ± 0.81	9.1 ± 5.97	*0.001

Independent sample t test used to compare age, BMI, duration of DM, HbA1c, LCR.

Chi square used to compare gender, p value< 0.05 statistically significant.

Table 2: *2 × 2 Contingency Table*

LCR (cut-off = 5.5 µg/g)	On the basis of ACR(30-300 mg/g)	
	Diseased n= 55	Non-Diseased n =15
Positive	TP (47)	FP (1)
Negative	FN (8)	TN (14)

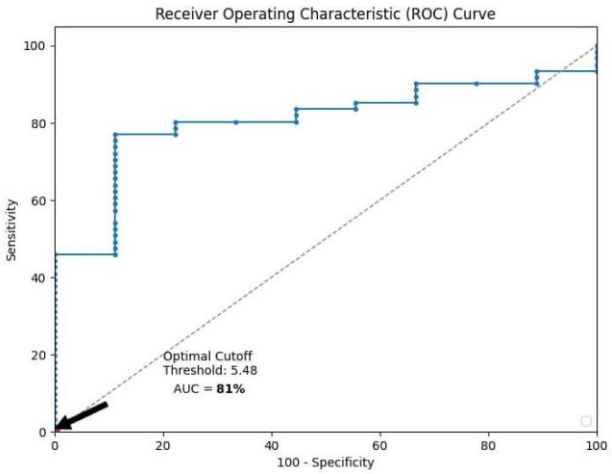

Figure 1: *ROC curve for LCR*

Discussion

Pakistan stands on third number in the world after China and India for the prevalence of DM. According to International Diabetes Federation (IDF) Report, 26.6% adults are affected by it[13]. The increased prevalence results in increased number of vascular complications. DN is the most frequent complication attributed to higher morbidity and mortality. Microalbuminuria is used as an early

marker of DN.[14-16] However, a number of diabetics develop decline in renal functions without microalbuminuria challenging the traditional theory that albuminuria precedes decline in renal function[17]. It is therefore necessary to find a better or an adjuvant marker along with the ACR for early prediction of DN. Various novel urinary markers, mainly produced by renal proximal tubular cells are being explored to predict DN at an earlier stage.[7,8]

The diagnostic accuracy of L-FABP, one of the renal tubular proteins, was determined in this study. Total 70 diabetics were enrolled; 55 and 15 were labeled as DN and non-DN respectively on the basis of ACR. Using 5.5 µg/g cut off value for LCR in our study, Sn, Sp, PPV, NPV, Youden's index and overall DA was 85.5%, 93.3%, 0.98, 0.6 ,0.78 and 0.87 respectively. The results are in agreement with the study of Ngan et al to compare role of L-FABP with ACR for early prediction of nephropathy in T2DM patients.[7] The difference is the cut off value LCR = 5.0 µg/g Cr used in their study. The results of our study are also supported by the studies conducted in Japan, Finland and Egypt.[18-20]

There was female predominance in our study subjects indicating DM more common among females in our society. The findings are similar to study by Xia et al., 2021 but contradict the study of Lee et al.[21,22]

To the best of authors' knowledge, this study was one of the first studies conducted in Pakistan to determine the diagnostic accuracy LCR for DN. However, the study was performed on a small scale and the diagnostic accuracy of LCR was not compared with other renal tubular injury markers due to financial constraints. It is, therefore recommended to conduct multi-centric studies to establish its diagnostic role.

Conclusion

LCR has overall good diagnostic accuracy to diagnose renal damage in T2DM patients. It has the potential to either substitute or be used as an adjuvant biomarker of ACR for early prediction of DN for timely management in order to avoid consequences of irreversible renal loss.

Ethical Approval: The IRB/EC approved this study via letter no. UHS/Education/126-22/8049 dated 02-11-2022.

Conflict of Interest: *None*

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Authors' Contribution: Role and contribution of authors followed ICMJE recommendations

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