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Fatty Acid Binding Protein (1 & 2) as Markers of Diabetic Nephropathy in Elderly Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: The 15kDa cytoplasmic fatty acid-binding protein family (FABPs) is one of the most exciting novel indicators for the diagnosis of renal damage.

Objective: The aim of this study was to investigate the relation of circulating FABP1 and FABP2 levels as clinical and biochemical markers and varying stages of nephropathy in senior T2DM patients.

Patients and Methods: This case-control study included a total of 60 patients with Type 2 diabetes and 30 nondiabetic controls, attending and followed up at Out-Patient Clinics, Department of Internal Medicine, Zagazig University Hospitals. Patients were divided into 3 equal groups: Group I: healthy control group; Group II: diabetic group without incidence of diabetic nephropathy; Group III: diabetic nephropathy group. All patients were tested for FABP1 and FABP2. **Results:** FABP1 and FABP2 levels significantly varied among the study's three groups. The significance was referred to the higher expression of FABP1 and FABP2 in group II and III than controls and higher expression in group III than group II as illustrated in post-hoc analysis. There were significant positive Pearson correlations between FABP1, FABP2 and serum creatinine, serum urea, urine albumin-creatinine ratio (uACR) while the correlation between FABP1, FABP2 and eGFR was inverse correlation of significance.

Conclusion: It could be concluded that FABP1 and FABP2 may be novel biomarkers of diabetic nephropathy. FABP1 has an 87% sensitivity and an 83% specificity for the diagnosis of diabetic nephropathy at a cut-off value equal to 2.7 ng/dL. FABP2 has a 93% sensitivity and a 33% specificity for diagnosing diabetic nephropathy at a cut-off value equal to 0.16 ng/dL.

Keywords: Fatty Acid Binding Protein, Diabetic Nephropathy.

INTRODUCTION

The process of ageing itself is a major contributor to the high prevalence of many fatal illnesses among humans. About 100,000 individuals each day globally die from age-related illnesses [(1)].

Diabetic nephropathy (DN) is the most common form of chronic kidney disease and the leading cause of end-stage renal disease (ESRD). Type 2 diabetes, which is often brought on by overeating, is mostly to blame. Albumin excretion in the urine and the fall in Glomerular Filtration Rate are used to categorize the clinical progression of diabetic nephropathy [(2)].

A novel biomarker is required that would be part of the structural components of kidney. Many renal biomarkers have been researched for early prediction of renal damage. The 15kDa cytoplasmic fatty acid-binding protein family (FABPs) is one of the most exciting novel indicators for the diagnosis of renal damage [(3)]**.** One of the proteins involved in fatty acid metabolism is fatty acid-binding protein 1 (FABP1), also known as liver-type fatty acid-binding protein or L-FABP, a 14 kDa small molecule produced in the proximal tubules of the human kidney. This is because proximal tubule cell damage causes an increase in the circulating proportion of FABP1 to be filtered by the glomeruli and then reabsorbed in the proximal renal tubules [(4)].

The second type of fatty acid-binding protein (FABP2), also known as intestinal-type fatty acid-binding protein (I-FABP), is a small, water-soluble protein with a molecular weight of 14-15 kDa that is expressed by enterocytes from the duodenum to the ileum [(5)].Acute intestinal ischemia, such as necrotizing enterocolitis and nonocclusive mesenteric ischemia, can be diagnosed with the use of the biomarker FAs-associated peptide 2 (FABP2), which is released into the systemic circulation quickly in response to enterocyte damage. Similar to other FABP multigene family members, FABP2 is predicted to be swiftly removed by the kidneys (half-life of around 11 minutes)[(6)].

Tsai *et al.* [(7)] reported that FABP1 and FABP2 may be useful new biomarkers of diabetic nephropathy by examining their association with nephropathy in T2DM patients. FABP1 and FABP2 have been linked increasingly to the onset and progression of chronic renal disease. Almost no research was done on patients above 65.

The aim of this study was to investigate the relation of circulating FABP1 and FABP2 levels as clinical and biochemical markers and varying stages of nephropathy in senior T2DM patients.

PATIENTS AND METHODS

This case-control study included a total of 60 patients with Type 2 diabetes and 30 nondiabetic controls, attending and followed up at Out-Patient Clinics, Department of Internal Medicine, Zagazig University Hospitals.

Inclusion criteria: The geriatric population aged 65 years and above, male or female without diabetes. Elderly Type 2 diabetic patients without diabetic nephropathy, and elderly Type 2 diabetic patients with diabetic nephropathy

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Exclusion criteria: Subjects under 65 years old. Type 1 diabetic patients. Patients with chronic lung diseases, chronic otitis media, urolithiasis, liver cirrhosis, a urinary tract infection, congestive heart failure, pelvic infection, sinusitis, or chronic viral hepatitis.

Patients were classified according to presence of diabetes and proteinuria: Group I (Control group): No diabetes or proteinuria (30 patients). **Group II:** Type 2 diabetes without diabetes nephropathy (30 patients). **Groups III:** Type 2 diabetes with diabetic nephropathy.
All patients were submitted to a comprehensive clinical examination and history taking.

Lab investigations: Include any investigations that verify inclusion and exclusion criteria:

- Serum FABP1 and FABP2.
- Lipid profile (triglycerides, cholesterol, LDL, HDL).
- Liver function tests.
- Diabetes profile (Fasting blood glucose level, HbA1c.
- Renal function tests (serum creatinine, serum urea, eGFR and urinary albumin/creatinine ratio).

Ethical consent:
An approval of the study was obtained from Zagazig University Academic and Ethical Committee (IRB approval: #6732/14-2-2021). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In order to analyze the data acquired, Statistical Package of Social Services version 20 was used to execute it on a computer (SPSS). In order to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Table 1 shows the demographic data of participants (age, sex, BMI, and smoking habits). Patients with diabetic nephropathy had older age than the other 2 groups with statistically significance **(p value: 0.0001)**.

Table (1): demographic data:

	Group I (30 control)	**Group II (30 patients)**	**Group III (30 patients)**	**P value**
Age (years) Mean±SD	67±148	67.5±1.54	69.33±3.3	**0.0001**
Sex (male) No. (%)	15 (50%)	16 (53.3%)	18 (60%)	0.731
BMI (kg/m^2)	25.87±2.7	25.92±2.78	25.98±2.78	0.988
Smoking No. (%)	5 (16.7%)	6 (20%)	4 (13.3%)	0.787

Table 2 shows that there were a statistically significant differences between different groups regarding laboratory investigations according to post-Hoc analysis.Triglycerides, cholesterol, and LDL were significantly higher in group III while HDL was significantly lower compared to other 2 groups. Fasting blood sugar and HgbA1c were significantly higher among group III. Liver function tests were comparable among the 3 groups. serum creatinine, serum urea, and GFR showed statistically significant differences being serum creatinine and serum urea were higher and GFR was lower among group III than the other 2 groups (Table 2).

Table (2): Post-Hoc analysis of laboratory investigations:

	Groups I:II	**Group I:III**	**Group II:III**
Triglycerides	0.932	**0.001**	**0.0001**
Cholesterol	0.854	**0.0001**	**0.0001**
LDL	0.917	**0.0001**	**0.0001**
HDL	0.434	**0.0001**	**0.0001**
ALT	0.842	0.994	0.783
AST	0.595	0.997	0.549
FBS	**0.0001**	**0.0001**	**0.001**
Hgb A1c	**0.0001**	**0.0001**	**0.0001**
S. cr	0.54	**0.0001**	**0.0001**
eGFR	**0.0001**	**0.0001**	**0.0001**
Urea	0.835	**0.0001**	**0.0001**
UACR	**0.0001**	**0.0001**	**0.0001**

There was statistically significant difference among the 3 groups regarding levels of FABP1 and FABP2. The significance was referred to the high expression of FABP1 and FABP2 in group II and III than controls and also higher expression in group III than group II as illustrated in post-hoc analysis (Table 3).

Table (3): FABP1 & FABP2 among the studied groups:

	Group I (30 control)	Group II (30 patients)	Group III (30 patients)	P value
FABP1 (ng/dL) mean±SD	2.2±0.43	3.252±0.74	4.09±1.0	**0.0001**
FABP 2 (ng/dL) mean±SD	0.1±0.02	0.15±0.02	0.23±0.038	**0.0001**

FABP1 & FABP2 among the studied groups (post-Hoc analysis):			
Post-Hoc**	Groups I:II	Group I:III	Group II:III
FABP1 (ng/dL)	0.001	0.0001	0.04
FABP2 (ng/dL)	0.026	0.0001	0.0001

There was significant Pearson correlation between FABP1 and patient age. While, there was no statistically significant difference between FABP2 and patient age. There was significant positive Pearson correlation between FABP1, FABP2 and incidence of diabetes, diabetes duration, FBS and HgbA1C. Lipid profile and FABP1 had no significant correlation while lipid profile and FABP2 had statistically significant positive correlation. There was significant positive Pearson correlation between FABP1, FABP2 and s.cr, urea, UACR while the correlation between FABP1, FABP2 and eGFR was inverse correlation of significance. Regression analysis (adjusted model including all factors) was used to compare group II and III to detect factors associated with diabetic nephropathy in diabetic patients including FABP1 and FABP2 (Table 4).

Table (4): Correlation of FABP1 and FABP2 to clinical condition and different laboratory investigations:

	FABP1		**FABP2**	
	R	**P value**	**r**	**P value**
Age (years)	0.293	**0.005**	0.165	0.12
Sex (Male)	0.07	0.512	0.092	0.391
BMI (kg/m^2)	-0.068	0.526	0.088	0.409
Hypertension (mmHg)	0.206	0.05	-0.045	0.67
Diabetes	0.57	**0.0001**	0.472	**0.0001**
Diabetes duration	0.476	**0.0001**	0.237	**0.024**
Fasting blood sugar (mg/dL)	0.549	**0.0001**	0.444	**0.0001**
HgbA1c (mmol/mol)	0.434	**0.0001**	0.462	**0.0001**
Cholesterol (mg/dL)	-0.052	0.629	0.198	0.062
Triglycerides (mg/dl)	-0.238	0.024	0.428	**0.0001**
LDL (mg/dL)	-0.137	0.197	0.352	**0.001**
HDL (mg/dL)	0.251	0.017	-0.478	**0.0001**
S. creatinine (mg/dl)	0.557	**0.0001**	0.544	**0.0001**
eGFR	-0.545	**0.0001**	-0.561	**0.0001**
Urea (mg/dl)	0.474	**0.0001**	0.494	**0.0001**
UACR (mg/g)	0.609	**0.0001**	0.559	**0.0001**
FABP1 (ng/dL)			0.378	**0.0001**
FABP2 (ng/dL)	0.378	**0.0001**		

Regression analysis showed statistically significant difference between both groups regarding HgbA1c, Serum creatinine, urea, UACR and GFR. Also, FABP1 (p value: 0.04; 95%CI: -0.022 to 0.049) and FABP2 (p value: 0.03; 95%CI: -0.061 to 1.45) showed statistical significance (R: 36.24; adjusted R: 32.1; p value: 0.0001) (Table 5).

Table (5): FABP1 & FABP2 as markers for diabetic nephropathy (multivariate analysis between group II and III):

	B estimate	95% confidence interval		P value
		Lower	Upper	
Age (years)	-0.011	-0.021	0.017	0.823
Sex (male)	0.06	-0.037	0.159	0.215
Smoking	-0.043	-0.176	0.06	0.326
BMI (kg/m^2)	0.006	-0.017	0.019	0.91
Hypertension (mmHg)	0.014	-0.082	0.111	0.766
Diabetes duration	0.001	-0.01	0.01	0.973
Fasting blood sugar (mg/dL)	0.01	-0.001	0.004	0.838
HgbA1c (mmol/mol)	0.096	-0.001	0.001	**0.047**
Cholesterol (mg/dL)	-1.2	0.0001	0.009	0.379
Triglycerides (mg/dl)	0.146	-0.003	0.001	0.172
LDL (mg/dl)	-0.187	-0.015	0.003	0.099
HDL (mg/dl)	0.132	-0.008	0.012	**0.047**
S. creatinine (mg/dl)	-0.1444	-0.093	0.012	**0.047**
eGFR	-0.44	-.014	-0.002	**0.014**
Urea (mg/dl)	0.226	0.000	0.005	**0.032**
UACR (mg/g)	0.1	-0.001	0.002	0.559
FABP1 (ng/dL)	0.036	-0.022	0.049	**0.04**
FABP2 (ng/dL)	0.093	-0.061	1.45	**0.03**

At cut-off value equal to 2.7 ng/dL, FABP1 could be used to diagnose diabetic nephropathy with sensitivity (87%) and specificity (83%) **(Figure 1).**

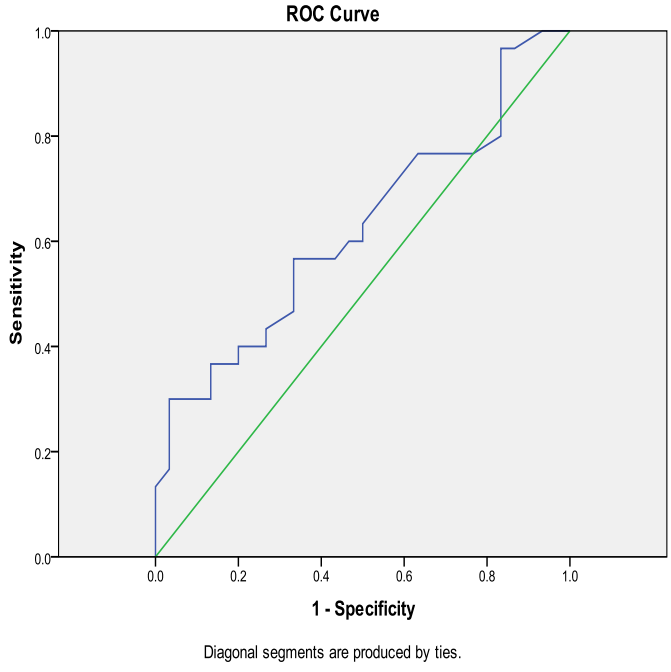

Figure (1): ROC analysis of FABP2 as a marker for diabetic nephropathy.

At cut-off value equal to 0.16 ng/dL, both the sensitivity (93%) and specificity (97%) of FABP2 for the diagnosis of diabetic nephropathy have been demonstrated (33 percent) **(Figure 2).**

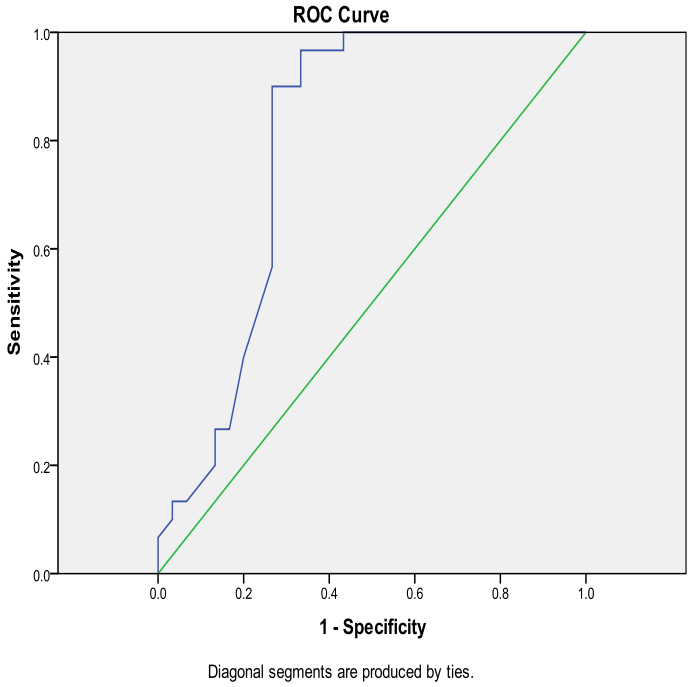

Figure (2): ROC analysis of FABP2 as a diabetic nephropathy marker.

The levels of FABP1 and FABP2 in the whole group and in group 1 individually did not differ significantly between patients with hypertension and those without hypertension. There was no significant difference in FABP1 levels between the hypertension and non-hypertension groups in group 2, however there was a significant difference in FABP2 levels (p= 0.002). In group 3, The levels of FABP1 were significantly different between those who had

hypertension and those who did not.(p=0.043) However, no statistically significant difference in FABP2 levels could be seen between the two groups (Table 6).

Table (6): Effect of hypertension on FABP1 and FABP2 in total cohort and each group separately:

	Hypertension Mean±SD	No hypertension Mean±SD	P value
Total Cohort			
FABP 1	3.33± 0.74	2.9± 0.41	0.23
FABP 2	0.16± 0.03	0.16± 0.02	0.73
In group 1			
FABP 1	2.18± 0.33	1.9±0.31	0.69
FABP 2	0.12± 0.02	0.11± 0.02	0.99
In group 2			
FABP 1	3.56± 0.71	2.84± 0.64	0.07
FABP 2	0.12± 0.02	0.19± 0.02	**0.002**
In group 3			
FABP 1	3.55± 0.71	4.63± 0.84	**0.043**
FABP 2	0.22± 0.03	0.23± 0.04	0.67

DISCUSSION

All persons with diabetes should be screened once a year with ACR for moderate (A2) albuminuria, as recommended by the ADA, NICE, and EASD, with follow-up testing required if abnormal findings are found. Care should be exercised when evaluating change between two assessments; looking at serial trends is more trustworthy. This biological variance in ACR readings should also be taken into account when monitoring serial changes or response to therapy [8].

Analysis of urine FABP1 in relation to histological damage score showed that it was more sensitive and specific than BUN and urinary NAG in detecting acute tubular necrosis in many animal models of acute kidney injury [9].

However, few research have looked at how FABP1 and FABP2 function as indicators of renal injury in persons with diabetes. Therefore, we set out to assess the reliability of FABP1 and FABP2 as diagnostic indicators for diabetic nephropathy and as predictors for the onset of diabetes in diabetic individuals.

In the current study there was statistically significant difference between the 3 groups regarding patient age as diabetic nephropathy patients had older age than the other 2 groups. This comes in agreement with a study by **Russo *et al.*** [10] who reported increased eGFR and albuminuria in elderly diabetic patients.

Our results did not found a correlation between patient gender and incidence of diabetic nephropathy. Similar to our results, some studies challenged the presence of gender differences between diabetic nephropathy and non-diabetic nephropathy patients and stated that no difference was found between males and females [11].

When comparing the three groups, there was no discernible trend toward smoking. Similarly, individuals with type 2 diabetes mellitus who smoked in the past or who now smoke showed a favorable correlation with eGFR reduction [12].

Diabetic nephropathy patients had the poorest mean values for triglycerides, cholesterol, LDL, and HDL, whereas the control group had the best mean values for lipid profile examinations, indicating a statistically significant difference between the groups. In accordance with our study, dyslipidemia performed as a risk factor for albuminuria and diabetic kidney disease, with adjusted ORs of 1.29 and 2.51, respectively in a Chinese study [13].

Fasting blood glucose levels and Hemoglobin A1/C had higher mean values among diabetic nephropathy patients than control group and diabetic group without diabetic nephropathy. In agreement with this findings, **Elley *et al.*** [14] reported presence of positive correlation between progression to diabetic nephropathy and persistent elevated FBS and HgB A1C.

Regarding FABP1 and FABP2 levels, there were statistically significant differences between the 3 groups as their levels were higher among diabetic nephropathy patients than the other 2 groups. Thus, FABP1 and FABP2 could be considered as biomarkers for renal insult among diabetic patients.

Regarding FABP1 as a marker of incidence of renal insult or diabetic nephropathy, at cutoff equal to 2.7, FABP1 exhibited 87% sensitivity and 83% specificity in prediction of incidence of diabetic nephropathy. Our results came in agreement with previous human studies. **Suzuki *et al.*** [15] conducted his study on 356 diabetic patients divided according to the degree of albuminuria and he found a significant association between the stage of diabetic nephropathy and FABP-1.

Panduru *et al.* [16] also found significant correlation between FABP-1 and incidence of proteinuria. He also, correlated the levels of FABP1 to disease progression from non proteinuric to microalbuminuric then to clinical albuminuric and also to progression to end stage renal disease. He found no difference between FABP1 and albumin creatinine ratio regarding their accuracy as diagnostic models for diabetic nephropathy by receiver operator characteristic testing with comparable area under curve (AUC). Similarly, **Kare *et al.*** [6] found statistically significant difference between diabetic nephropathy patients and diabetic patients without nephropathy regarding FABP1 levels in his study which was conducted on 84 patients and included healthy

individuals also.

Of note, FABP1 also was higher among diabetic patient without diabetic nephropathy than healthy control group. **Kare *et al.* [6]** also reported higher FABP1 levels among diabetic patients even without nephropathy than healthy controls.

Regarding FABP2 as a marker of incidence of renal insult or diabetic nephropathy, at cutoff equal to 0.16, FABP1 exhibited 93% sensitivity and 33% specificity in prediction of incidence of diabetic nephropathy. In agreement with the current study, **Tsai *et al.* [7]** reported statistically significant difference between nephropathy and no nephropathy groups regarding FABP2 and FABP2 showed sensitivity of 48.2% and specificity of 85.6% in diagnosis of diabetic nephropathy**.**

In the current study, there was statistically significant positive correlation between FABP1, FABP2 and age but no correlation was found with BMI. **Tsai *et al.* [7]** found the same correlation with age but also statistically significant correlation with BMI.

There was positive correlation between FABP and diabetes duration, fasting blood glucose and hemoglobin A1C. In agreement with this result, **Kare *et al.* [6]** concluded the same correlations. In contrary to this study, no correlation was found between FABP and FBS, HbA1c in a study by **Tsai *et al.* [7]** however he did not include non-diabetic healthy control patients in his study**.** There was statistically positive correlation between FABP1 & 2 and serum creatinine or proteinuria and negative correlation with e GFR. In accordance with these results, **Mou *et al.* [17]** reported the same associations with statistically significant difference.

There was also positive correlation between FABP2 and triglycerides and LDL but nor with cholesterol while in **Tsai *et al.* [7]** there was statistically significant correlation with cholesterol.

Multivariate analysis for predictors of diabetic nephropathy in the current study statistically significant difference between both groups regarding HgbA1c, S.cr, urea, UACR and GFR. Also, FABP1 (p value: 0.04; 95%CI: -0.022 to 0.049) and FABP2 (p value: 0.03; 95% CI: -0.061 to 1.45) showed statistical significance. In agreement with these findings, **Mou *et al.* [17]** found in his multivariate analysis statistically significant differences regarding s. creatinine and FABP1.**Tsai *et al.* [7]** proposed in his multivariate analysis that Age, gender, BMI, SBP, DBP, fasting glucose, lipid profile, smoking status, FABP1 and FABP2 are considered statistically significant predictors for diabetic nephropathy among diabetic patients.

CONCLUSION

It could be concluded that FABP1 and FABP2 may be novel biomarkers of diabetic nephropathy. FABP1 has an 87% sensitivity and an 83% specificity for the diagnosis of diabetic nephropathy at a cut-off value equal to 2.7 ng/dL. FABP2 has a 93% sensitivity and a 33% specificity for diagnosing diabetic nephropathy at a cut-off value equal to 0.16 ng/dL.

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Author contribution: Authors contributed equally in the study.

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