Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13058
DOI URL: http://dx.doi.org/10.21474/IJAR01/13058

RESEARCH ARTICLE

CORRELATION BETWEEN FATTY BINDING PROTEIN 1 (FABP1) AND DIABETES TYPE 2 (T2DM)

Sofia Ashraf Abd-Elhady[1], Asmaa Mohamed Mansour[2], Hassan Shalby[3], Naglaa Fawazy[4], Yasser Sakr[4], Abeer A. Barakat[5], Hala H. Eldeeb[6], Ahmed Sobhy Adaroas[7], Wafaa Salah[8], Amina S. Soliman[9] and Mohamed Ramdan Ezz AL Arab[10]

1. Misr University for Science and Technology, Egypt.
2. Division of Biochemistry, Chemistry Department, Faculty of Science, Fayoum, Egypt.
3. Internal Medicine Department, Faculty of Medicine, Misr University for Science and Technology, Egypt.
4. Clinical and Chemical Pathology Department, National Institute of Diabetes and Endocrinology, Egypt.
5. Biochemistry Department, National Hepatology & Tropical Medicine Research Institute.
6. Clinical and Chemical Pathology Department, El Sahel Teaching Hospital.
7. Clinical and Chemical Pathology Department, El Sahel Teaching Hospital.
8. Internal Medicine, National Institute of Diabetes and Endocrinology, Egypt.
9. Nutrition and Food Science,National Institute of Diabetes and Endocrinology.
10. Hepatology Department, Ahmed Maher Teaching Hospital, Cairo, Egypt.

Manuscript Info

Manuscript History
Received: xxxxxxxxxxxxxxx
Final Accepted: xxxxxxxxxxxx
Published: xxxxxxxxxxxxxxx

Key words:
T2DM, FABP1, Correlation, Biomarker

Abstract

Background: Diabetes mellitus is best described as a condition that is characterized by postprandial hyperglycemia that has two types; diabetes type 1 and diabetes type 2. Many patients with type 2 diabetes can be asymptomatic. There are many biomarkers were assessed for the detection of diabetes type 2.

Aim: The aim of the study was to investigate the concentration pf FABP1 in Patients with diabetes type 2 and healthy control.

Methods: Samples were collected from 99 diabetic patients and 85 samples of healthy participants as the control group. All participants were subjected to liver enzymes (ALT and AST) lipid profile (triglycerides, HDL, LDL, and cholesterol), T-billirbun, Alp, AFP, S-creatinine, Hb, F. Insulin, and CA19.9 that were done by an autoanalyzer. The serum level of fatty acid-binding protein 1 was measured by SunRed human FABP1 Elisa kits.

Results: Data was represented as mean ± standard deviation or median with statistically significant values of glucose, lipid profile markers, FABP1, and CA19.9 (at P< 0.05). Findings revealed a significant positive correlation between our marker FABP1 and TG, cholesterol, Fasting insulin, and negative coreelation with WBCs.

Conclusion: FABP1 was increased in patients with diabetes type 2 and showed high sensitivity, and specificity for the detection of patients with type 2 diabetes mellitus.

Corresponding Author:- Sofia Ashraf Abd-Elhady
Address**:** Misr University for Science and Technology, Egypt.

Introduction:

Diabetes mellitus is best described as a condition that is characterized by inappropriate fasting or postprandial hyperglycemia; its metabolic effects, including impaired protein and fat metabolism **(Barnett, 2005)**. The disorder has two main manifestations **(ADA, 2010)**. Type 1 diabetes is normally caused by autoimmune disruption of the pancreatic islets of Langerhans. Antibodies are exist in the serum of patients with type 1 diabetes, including insulin itself, to many components of the islets of Langerhans **(Loura and McEntyre, 2004)**. Type 2 diabetes is much more common, accounting for about 90 percent of all cases than type 1 diabetes **(Goyal and Jialal, 2019)**. The dietary guidelines are important for diabetic patients as proper nutrition is a pivotal factor in the practical treatment of type 2 diabetes. The nutrition recommendations help the slowing of diabetes progression **(Pegklidou et al, 2010).** Many patients with type 2 diabetes are asymptomatic; however, when regular measurements are performed, they show elevated blood glucose levels, they are also diagnosed with type 2 diabetes **(ADA, 2004).** Biomarker refers specifically to a function that is indicated as a sign of a therapeutic presence of pathogenic processes, natural biological processes, and pharmacological responses **(Mayeux, 2004)**. Biomarkers are including, α-hydroxybutyrate, Peroxisome proliferator-activated receptor, Fructosamine, Carcinoembryonic antigen, Carbohydrate antigen 199, Glycated Haemoglobin, Fetuin-A and Ferritin, transferrin, and the mammalian FA-binding proteins (FABPs) bind long-chain FA. All FABPs bind both saturated and unsaturated long-chain FA **(Richieri*et al.*, 2000)**. There're many types of fatty acid-binding proteins such as FABP2, FABP3, FABP4, FABP5, FABP6, FABP7, and FABP1. **(Wang *et al.*, 2015)**. The gene ablation of FABP1 was found to affect the high-fat diet, where the gene ablation was found to diminish the effect of high fat diet on brain endocannabinoid levels **(Martin et al, 2017).** FABP1 may be a new diagnostic marker for the diagnosis of liver injury **(Akbal*et al*., 2013)** and a marker of diabetic nephropathy **(Tsai *et al.*, 2020).** The objective of the current study is to investigate FABP1 in Patients with diabetes type 2, and to find the correlations between FABP1 and fasting insulin in these patients .

Subjects and Methods:

The study was conducted on two groups; 99 diabetic patients as a patient group and 85 healthy participants as the control group in the duration from November 2020 to February 2021.We excluded patients with any infection, including viral hepatitis, autoimmune disease, cardiovascular disease, diabetes-related complications including proliferation retinopathy, autonomic neuropathy, diabetes type 1, pregnancy, alcohol consumption, and cigarette smoking.

7 ml of blood was collected from each patient in clean dry tubes and left for 15 minutes at room temperature to clot then centrifuged at 3000 xg for 15 minutes in a cooling centrifuge, the serum was used for the determination of several laboratory investigation. For the determination of white blood cells; 2 ml of whole blood was collected in plastic tube containing EDTA as anticoagulant.

All participants were subjected to liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT)), lipid profile (triglycerides, HDL, LDL, Cholesterol), glucose, fasting insulin (for calculation of insulin resistance), gamma-glutamyl transferase (GGT), total bilirubin, creatinine, hemoglobin (Hb), alpha-fetoprotein (AFP), carcinoantigen 19.9 (CA19.9) and anthropometric measures for body mass index (BMI) and all the previous parameters were assayed. Serum level of fatty acid-binding protein 1 was measured by SunRed human FABP1 Elisa kits catalog No. 201-12-2160. The study duration was from November 2020 to February 2021, an informed consent was obtained from each participant before participating in this study.

Statistical analysis:

SPSS program version 21 was used to analyze the data; qualitative data was represented as number and percents, whereas the quantitative data was represented using mean and standard deviation. Receiver operating characteristic curve was used to determine the sensitivity, specificity, positive and negative predictive values and the area under curve. P-value at ≤ 0.05 was considered significant.

Results:

Table (1) showed the comparison between group (1) (Diabetic patients) and group (2) control group regarding the age, gender, and BMI whereas table (2) shows the laboratory investigations of ALT, AST, ALP, creatinine, glucose, cholesterol, Tg, HDL, LDL, fasting insulin, CA19.9, and WBCs. There were significant differences in demographics (age, gender, and BMI). Regarding laboratory investigations there were significant differences between the two groups regarding the mean level of glucose, cholesterol, TG, HDL, LDL, FABP1, GGT, fasting insulin, Hb and CA19.9. The diabetic groups significantly showed higher mean levels of glucose, cholesterol, TG, LDL, GGT,

fasting insulin, FABP1 and CA19.9. On the other hand, there were no significant differences between the two groups under studying regarding the mean levels of ALT, AST, ALP, total bilirubin, creatinine, AFP, and WBCs.

Table 1: Demographic features of diabetic patients and control.

Characteristics	**Group 1** Diabetic pateints	**Group**2 Control	**P-value**
Age (years)	57.92 ± 9.01	55.53 ± 9.64	0.02*****
Gender **Male** **Female**	 53 (53%) 47 (47%)	 50(50%) 50(50%)	0.02*
BMI	32±3.7	27±2.4	0.005

Data are presented as mean ± standard deviation or median with Values statistically significant (at P< 0.05).

Table 2: The laboratory investigations of the two studied groups.

Variables	**Group 1** Diabetes	**Group**2 Control	**P-value**
ALT (IU)	34.97	24.8	0.45
AST(IU)	36.2	12.7	0.74
ALP (IU)	174.95 ± 121.36	167.17 ± 121.3	0.22
Total Bilirubin (mg/dl)	1.00	0.9	0.57
Glucose (mg/dl)	179±45.5	93±28	0.001*
Cholesterol (mg/dl)	198.3 ± 27.8	148.1 ± 18.8	0.000*
Creatinine mg/dl	0.96±0.52	0.73±0.4	0.33
TG (mg/dl)	171.1 ± 34.2	145 ±21.3	0.000*
FABP1 (P mol/L)	57±7.8	40 ±3.6	0.007*
HDL (mg/dl)	38.4 ± 9.6	43.8 ± 9.7	0.000*
LDL (mg/dl)	130±20.5	107.9 ± 10.99	0.000*
AFP (ng/ml)	4.7 ± 1.7	5.96 ± 2	0.4
GGT (U/L)	37±9.9	34 ± 9.2	0.02*
Fasting-insulin (mg/dl)	17.5 ± 9.3	3.1±1.2	0.000*
Hb (g/dl)	11.1 ± 1.1	11.9 ± 1.7	0.000*
WBCS (c/mm)	7321±3835	7196±2270	0.8
CA19.9 (U/ml)	44±5.3	33±7.3	0.04

Data are presented as mean ± standard deviation or median with; ALT: Alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TG: Triglyceride; FABP: Fatty Acid binding protein; HDL: High density lipoprotein; LDL: Low density lipoprotein; AFP; Alpha-fetoprotein; GGT; Gamma-glutamyl transferase; Hb: Hemoglobin; WBCs; White blood cells; CA; Carcinoantigen; *: Values statistically significant (at P< 0.05).

The Receiver Operating characteristic (ROC) curve of FABP1 for early detection of diabetes type 2 revealed that the area under the curve (AUC) was 85.7% (P<0.0001) **(figure1)**. The concentration of FABP1 was associated with T2DM patients, with a sensitivity of 93.3% and specificity of 80%, which means that FABP1 level increase parallels with T2DM patients (Table2).

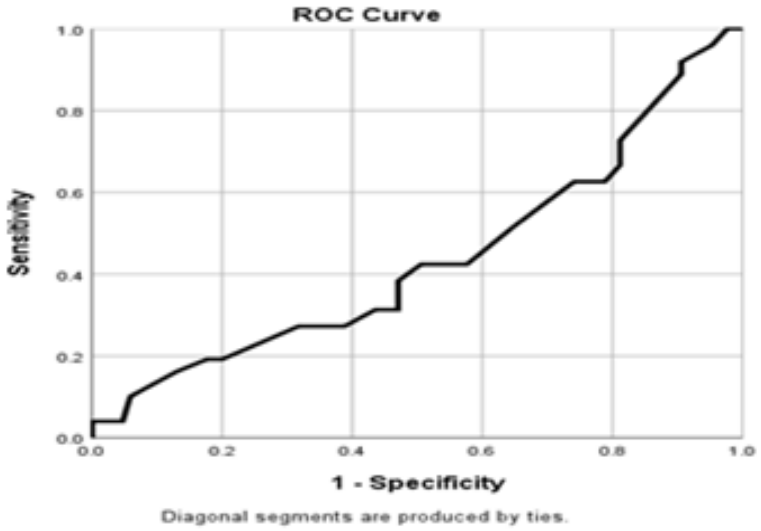

Fig1: The Receiver operating characteristic curve of FABP1.

Table 3: The Receiver operating characteristic curve of FABP1.

Test	Cut-off value	Sensitivity%	Specificity%	PPV %	NPV %	AUC%	P-value
FABP1(P mol/L)	**47**	**93.3**	**80**	**99**	**93.7**	**85.7**	**0.000***

PPV=positive predictive value; NPV=negative predictive value; AUC=area under curve*:Values statistically significant (at P< 0.05).

In table (3), results showed that there were significant positive correlations between our marker FABP1 and each of TG, cholesterol, and fasting insulin, while there is a negative correlation with WBCs.

Table 4: Correlation coefficient of FABP1 and routine Parameters.

Correlation **FABP1** vs	r
T**G (mg/dl**)	0.250*
Cholesterol **(mg/dl)**	0.232*
HDL **(mg/dl)**	0.178
LDL **(mg/dl)**	0.105
CA19 9 **(U/ml)**	0.117
FASTING INSULIN **(mg/dl)**	0.296**
WBCs **(c/mm)**	-0.283**

* Significant correlation, ** high Significant correlation

Discussion:

Fasting hyperglycemia is a characterization of diabetes mellitus and it has metabolic effects, including impaired protein and fat metabolism. This disorder has two main manifestations diabetes type 1 and types 2. Type 2 diabetes occurs when your body's cells resist insulin's normal effect of driving glucose from the blood into the cells' interiors. Insulin resistance is the medical term for type2 diabetes mellitus disease. As a result, glucose levels in the blood begin to rise. Biomarkers are classified into two categories: standard and novel biomarkers. In this study, we investigated one biomarker from the Fatty acid-binding protein family, which is fatty acid-binding protein 1 to detect patients with diabetes type 2.

In our study, we found that the increase in the level of glucose in the blood is mainly responsible for the observed hyperglycemia. Also, there were significant increases in the level of total cholesterol, LDL cholesterol, triglycerides with a significant decrease in HDL cholesterol in the blood among the patient group compared to the control. Regarding the activities of liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase

(ALT), the increase in their levels among the patient group wasn't significant. However, the increase in liver enzymes is an indicator of hepatocellular injury and is also associated with insulin resistance.

Previous studies showed that type 2 diabetes was associated with a clinical spectrum of liver abnormalities such as increasing levels of GGT, ALT, and ALP in the patients **(Balogun, 2008).** In addition, the study by **(Sanyal *et al.*, 2015)** results has demonstrated that abnormal liver function (including increased levels of liver enzymes ALT and GGT) was frequently associated with type 2 diabetes mellitus. In agreement with the previous study, our study showed that GGT was increased among diabetic patients significantly. Our findings are consistent with those of previous studies, which have indicated that diabetes is associated with elevated lipolysis, triglyceride synthesis, and hepatic uptake of free fatty acids, and with an accumulation of hepatic triglycerides due to insulin resistance **(Pagano, 2002).** The results of the current study showed that levels of WBCs and differential leukocyte counts were slightly increased in T2DM patients compared to controls, with no remarkable difference. The study by **(Vozarova*et al.*, 2002)** showed that there was a relationship between WBC and diabetes mellitus as a result of increased inflammatory mediators. Inflammatory agents, insulin, and human blood components form a critical signal for any abnormalities, resulting in an invasion by foreign agents and/or inflammation **(Ohshita *et al.*, 2004).** However, we didn't find this association as the increased levelof WBCs in diabetic patients wasn't remarkable.

A research conducted by **(Anjaneyulu*et al.*, 2004)** reported that the serum creatinine in diabetic patients indicates progressive renal damage; this was in contrast to our findings, as the increase in creatinine level among diabetic patients wasn't significant. In another study, CA19-9 level was significantly higher in patients with diabetes compared with the control group; the level in diabetes group compared to control group was 19.5U/ml Vs. 7.4U/ml for diabetic and control group, respectively. Additionally, the prevalence of high CA 19-9 levels in patients with diabetes was 31.2% **(Kamile*et al.*, 2011).** Similarly, our study showed increase in the level of CA 19.9 in diabetes group compared to control group; however, the levels in our study in both groups were higher compared to the previous study. Moreove, the previous study showed that CA 19-9 level was positively correlated with age, and duration of diabetes **(Kamile*et al.*, 2011),** but we didn't assess such correlations in our study.

A study conducted by **(Tsai *et al.*, 2020)** showed that FABP1 levels were positively associated with creatinine and negatively associated with albumin and eGFR in patients with T2DM, but in our study we didn't evaluate such correlations. However, we found that FABP1 positively correlated with Tg (r=0.25), cholesterol (r=0.232), fasting insulin (r=0.296) and negatively correlated with WBCs (r=-0.283). Furthermore, they also found that higher plasma FABP1 and stages 3 and 4 of CKD classes in grade 2 or 3 of NAFLD was significantly observed compared to normal or grade 1 of NAFLD. FABP1 is expressed in both normal and diseased human kidneys, which indicated that FABP1 accurately reflected the severity of diabetic nephropathy and that it may be a suitable biomarker for the early detection of nephropathy in T2DM patients **(Kamijo-Ikemori*et al.*, 2009).**

Another study has shown that the plasma FABP1 concentration was significantly associated with nephropathy in T2DM patients even after controlling for anthropometric variables, fasting glucose, lipid profile, and smoking status. The increasing level of FABP1 showed a significant linear trend and and it was associated with nephropathy in T2DM patients**(Tsai *et al.*, 2020).** In another study, the results have shown that FABP1 was positively correlated with insulin resistance in human**s (Shi *et al.*, 2012).** In the current study, it was found that FABP1 was significantly and positively (r=0.296) associated with increased levels of fasting insulin indicating that FABP1 is associated with insulin resistance.

Conclusion:

FABP1 showed high sensitivity, and specificity with perfect positive predictive value and high negative predictive value in the detection of patients with type 2 diabetes mellitus showing that it can be used for the detection of type 2 diabetes mellitus.

References:

1. **Akbal E, Köklü S, Koçak E, Çakal B, Güneş F, Başar Ö & Şenes M (2013).** Liver fatty acid-binding protein is a diagnostic marker to detect liver injury due to chronic hepatitis C infection. Archives of Medical Research, 44(1), pp.34-38.
2. **American Diabetes Association (2004).** Diagnosis and classification of diabetes mellitus. Diabetes care, 32(1), S62–S67.

3. **American Diabetes Association (2010).** Diagnosis and classification of diabetes mellitus. Diabetes Care, 33(4):e57, S62-S69.
4. **Anjaneyulu M, & Chopra K (2006**). Possible involvement of cholinergic and opioid receptor mechanisms in fluoxetine mediated antinociception response in streptozotocin- induced diabetic mice. European journal of pharmacology, 538(1-3), pp.80-84.
5. **Balogun W O, AdeleyeJO, Akinlade KS, & Adedapo KS (2008**). M.Frequent. Kuti. Occurrence of high gamma-glutamyl transferase and alanine amino transferase among Nigerian patients with type 2 diabetes. The African Journal of Medical Sciences. 3(7) , pp. 177-183.
6. **Barnett D, & Krall LP (2005).** In: The History of Diabetes. 14th ed. Joslin's Diabetes Mellitus, editor. Boston, Massachusetts: Lippincott Williams & Wilkins, pp.1-17.
7. **Goyal R, Jialal I, Nguyen M (2020)**. Diabetes Mellitus Type 2 In StatPearls.
8. **Kamijo-Ikemori A, Sugaya TT, Sekizuka A, Hirata K, Kimura K (2009).** Amelioration of diabetic tubulointerstitial damage in liver-type fatty acid-binding protein transgenic mice. Nephrol Dial Transplant. PP.24:788–800.
9. **Kamile G, Nas S, Ozdemir D, Ersoy R, Cakir B, & Gumus M (2011).** "CA 19-9 level in patients with type 2 diabetes mellitus and its relation to the metabolic control and microvascular complications." The American journal of the medical sciences 341, no. 1 PP.28-32.
10. **Loura D & McEntyre J (2004**). Introduction to Diabetes. In The Genetic Landscape of Diabetes.National Center for Biotechnology Information (US), Ch.1.
11. **Martin GG, Landrock D, Chung S, Dangott LJ, Seeger DR, Murphy EJ, Golovko MY, Kier AB & Schroeder F (2017).** Fabp1 gene ablation inhibits high-fat diet-induced increase in brain endocannabinoids. *Journal of neurochemistry*, *140*(2), pp.294-306.
12. **Mayeux R (2004).** Biomarkers: potential uses and limitations. NeuroRx, 1(2), pp.182-188.
13. **Ohshita K, Yamane K, Hanafusa M, Mori H, Mito K, Okubo M, Kohno N (2004).** Elevated white blood cell count in subjects with impaired glucose tolerance. Diabetes Care. 27(2), pp. 491-496 .
14. **Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N (2002**). Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: Further evidence for an etiologic association. Hepatology (Baltimore, Md.). 35(2), pp. 367-372.
15. **Pegklidou K, Nicolaou I &J Demopoulos V, (2010).** Nutritional overview on the management of type 2 diabetes and the prevention of its complications. *Current diabetes reviews*, *6*(6), pp.400-409.
16. **Richieri GV, Ogata RT, Zimmerman AW, Veerkamp JH & Kleinfeld AM (2000).** Fatty acid binding proteins from different tissues show distinct patterns of fatty acid interactions. Biochemistry, 39(24), pp.7197-7204.
17. **Shi J, Zhang Y, Gu W, Cui B, Xu M& Yan Q (2012).** Serum liver fatty acid binding protein levels correlate positively with obesity and insulin resistance in Chinese young adults. PLoS One.PP.7:7(11):e48777.
18. **Tsai IT, Wu CC, Hung WC, Lee TL, Hsuan CF, Wei CT, Lu Y, Chung MF, Lee YJ & Wang CP (2020).** FABP1 and FABP2 as markers of diabetic nephropathy. International journal of medical sciences, 17(15), pp. 2338–2345.
19. **Vozarova B, Weyer C, Lindsay RS, Pratle RE, Bogardus C & Tataranni P (2002).** High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 51(2), pp. 455-461.
20. **Wang G, Bonkovsky HL, de Lemos A & Burczynski FJ (2015).** Recent insights into the biological functions of liver fatty acid binding protein 1. Journal of lipid research, 56(12), pp.2238-224.