Original Article

A Role Of Fabp1 And Eus As Diagnostic Tools For Pancreatic Steatosis

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Abstract

Background: Pancreatic steatosis recently gain attention due to its relationship to metabolic disease and pancreatic cancer. The need for a non-invasive marker that can be utilized to aid in diagnosis is essential to add to the investigations, especially when used with imaging such as endoscopic ultrasound(EUS). Fatty acid binding protein 1 (FABP1) is a tissue-specific marker that can be used to diagnose NAFPD.

Objective: The purpose of the current study was to determine the prevalence of NAFPD in obese and non-obese Egyptians with or without diabetes, evaluate any possible relationships between obesity, diabetes, or other metabolic risk factors, correlate pancreatic steatosis with non-alcoholic liver disease(NAFLD), and evaluate the diagnostic utility of FABP1 and EUS.

Patients and methods: A prospective cohort study included 120 patients aged 18-70 years, who attended the outpatient clinic of the gastroenterology, hepatology, and Infectious Diseases Department at Al-Azhar University Hospital (Cairo) from January 2022 to October 2020. Patients were divided into 4 equal groups: Group 1: Healthy individuals with normal BMI and non-diabetic, Group 2: Patients with normal BMI, diabetics or impaired fasting blood glucose, Group 3: Patients with BMI over 25 non-diabetics, and Group 4: Patients with BMI over 25, diabetics or impaired fasting blood glucose level.

Results: There was a positive correlation between FABP1 and pancreatic echogenicity, pancreatic steatosis is strongly associated with fatty liver and other metabolic risk factors.

Conclusion: There is a strong link between pancreatic steatosis, metabolic syndrome, and NAFLD. EUS is superior in assessing pancreatic steatosis and has the potential to improve patient outcomes. As a biomarker, FABP1 can be used for non-alcoholic fatty pancreatic disease.

Keywords: FABP1, Endoscopic ultrasound, Pancreatic steatosis,

Introduction

In the absence of heavy alcohol consumption, pancreatic steatosis is defined by fat accumulation in the pancreas that is mostly caused by obesity and metabolic syndrome. Congenital disorders, medications, or viral infections are possible additional etiological factors (1).

Ogilvie (2) was the first to describe non-alcoholic fatty pancreas disease(NAFPD). He evaluated obese patients and observed that 17% of them had pancreatic fat compared to 7% of the slim patients. Olsen examined 394 autopsied patients in 1978 and discovered that the amount of pancreatic fat increased with age (3). Similarly, Stamm demonstrated an increase in pancreatic fat with increasing age (4). They also discovered a link between pancreatic steatosis and the risk of developing type 2 diabetes mellitus (DM-T2) and atherosclerosis when the fatty content of the pancreas is 25% or higher

Van Geenen et al. proposed in 2010 that obesity and its association with insulin resistance play an important role in pancreatic adipocyte infiltration, leading to gland steatosis. Insulin resistance also

causes peripheral lipolysis, which results in a fatty acid flux into the hepatic parenchyma and the onset of nonalcoholic fatty liver disease (NAFLD) (5).

There are 2 mechanisms leading to fatty accumulation in the pancreas. The first is the death of acinar cells and their substitution by adipocytes. In this case, the state is called "fatty replacement". The second is fatty accumulation (6).

NAFPD prevalence has been recorded in both Asian and Western nations. Wang et al. stated that 16% of the Chinese population in Taiwan had a fatty pancreas (7). Male gender, age over 60, hypertension, fasting blood sugar, triglycerides, body mass index, central obesity, and NAFLD are all known risk factors for NAFPD in the general population (8).

It has been demonstrated that a fatty pancreas correlates with metabolic risk variables and may be a significant marker of metabolic syndrome. Epidemiology studies show that obesity increases the risk of pancreatic cancer (9).

Various imaging techniques are used to determine the amount of pancreatic fat, such as ultrasonography, computed tomography (CT), and MRI (9). Endoscopic ultrasonography (EUS) is an invasive endoscopic technique that offers very good visibility and assessment of the gland being investigated. The evaluation of texture in the pancreatic parenchyma is quite exceptional. The increased echogenicity of pancreatic parenchyma is not always the image of an increased fatty presence in the pancreas, but it can be caused by the presence of pancreatic fibrosis, which is considered a method limitation (10).

It is important to include a laboratory marker that may be utilized as a simple, non-invasive biomarker to aid in the diagnosis, particularly when imaging is involved. Fatty Acid Binding Protein 1 (FABP1) is a tissue-specific marker that can be utilized to identify NAFPD (11).

The purpose of the current study was to determine the prevalence of NAFPD in obese and non-obese Egyptians with or without diabetes, evaluate any possible relationships between obesity, diabetes, or other metabolic risk factors, correlate pancreatic steatosis (NAFPD) with non-alcoholic liver disease, and evaluate the diagnostic utility of FABP1 and EUS.

Patients and methods

From January 2022 to October 2022, 120 patients aged 18 to 70 years attended the hepatology and gastroenterology clinic at El-Hussein and Sayed Galal Hospitals(Al-Azhar University Hospitals in Cairo). They were split into four equal groups: Group 1: A seemingly healthy individual with a normal BMI who is not diabetic. Group 2 includes patients with normal BMI, diabetics, or impaired fasting blood glucose levels; Group 3 includes patients with BMI over 25, non-diabetics; and Group 4 includes patients with BMI over 25, diabetics, or impaired fasting blood glucose levels. Criteria for exclusion include a daily alcohol intake > 20gm and advanced Co-morbid illness. Written informed consent from all patients enrolled in the study, Full history and examination were done, and Body mass index was calculated according to (BMI) = weight (Kg)/ height (meter2). Laboratory investigation includes:

- Complete blood count (CBC).
- Fasting blood sugar(FBS),Post-prandial(PP-BS) and HbA1c%.
- HCV antibody and HBs antigen.
- Liver function tests include ALT, AST, ALP, GGT, serum bilirubin, and serum albumin.
- Lipid profile including cholesterol, triglycerides, HDL, and LDL.

The degree of liver steatosis was measured during abdominal ultrasound(US) examinations, and was classified into 4 grades (12):

Grade 0: normal liver echogenicity as compared to the right kidney.

.Grade 1: a slight increase in liver echogenicity with no attenuation in the far field.

Grade 2: a moderate increase in liver echogenicity with light attenuation in the far field and the diaphragm and vessels visible.

Grade 3: a substantial increase in liver echogenicity with poor visualization of the diaphragm and the vessels.

NAFLD was diagnosed when the liver appeared as grade 1 to 3.

*During EUS, the pancreas echogenicity was compared to the spleen and left kidney, and it was also graded (10), (13):
Grade 0: The pancreas, was isoechoic like the spleen and left kidney
Grade 1: The pancreas' echogenicity was slightly higher than the kidney and spleen.
Grade 2: A significant increase in pancreatic echogenicity, but less than retroperitoneal fat echogenicity.
Grade 3: the pancreas echogenicity was comparable to or greater than that of the retroperitoneal fat.
NAFPD was discovered when the pancreas showed signs of grades 1 to 3.
*Fatty Acid Binding protein1 (FABP1) which had been evaluated by the enzyme-linked immunosorbent assay (ELISA)
The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for the Social Sciences). Qualitative data were described using numbers and percentages. Comparison between different groups regarding categorical variables was tested using the Chi-square test. Quantitative data were described using mean and standard deviation. P value was used to explain the level of significance as follows: P value more than 0.05 non-significant, P value less than 0.05 significant, and P value less than 0.01 highly significant. The ROC curve is used to detect a cutoff of a certain outcome.

Results

There was a significant difference between groups regarding BMI. There was no significant statistical difference between groups as regard age and sex (Table 1).

Table (1): Comparison between different studied groups regarding basic

GroupsParameters	Group(1)(n=30)	Group(2)(n=30)	Group(3)(n=30)	Group(4)(n=30)	P
Age (years)					
Range	35.00-47.00	34.00-58.00	36.00-55.00	36.00-55.00	>0.05
mean +SD	41.20±6.46	43.15±11.86	45.95±5.28	44.35±5.17	
Gender					
Male Female	10 (50.0%)	12 (60.0%)	9 (45.0%)	6 (30.0%)	>0.05
	10 (50.0%)	8 (40.0%)	11(55.0%)	14 (70%)	
BMI (kg/m2)					
Range	21.00-24.50	21.00-24.50	26.30-34.00	26.30-36.30	<0.001
mean +SD	23.16±0.96	23.16±0.92	29.73±2.18	32.31±2.67	
P1		>0.05	0.0036*	0.001*	
P2			0.0029*	0.001*	
P3				>0.05	
Current smoking	4 (40.0%)	6 (30.0%)	6 (30.0%)	5 (25.0%)	>0.05
Systolic blood pressure (mmH)					
Range	25.0-135.0	25.0-138.0	25.0-135.0	25.0-138.0	>0.05

mean +SD	121.75±23.36	125.05±23.99	121.60±23.34	124.90±23.94	
Diastolic blood pressure (mmHg)					
Range	65.00-85.00	60.00-85.00	60.00-85.00	65.00-85.00	>0.05
mean +SD	77.00±5.71	68.50±7.96	68.30±6.91	77.50±5.74	
Hepatomegaly	1 (5%)	2 (10%)	1 (5%)	3 (15%)	>0.05

P1 compares group 1 and other groups, P2 compares group 2 and other groups, and P3 compares groups 3 and 4.

There was a significant statistical difference between groups as regard ALT, AST, and GGT (0.001, 0.002, and 0.001). There was a significant difference between groups concerning triglycerides (p-value < 0.001) (Table 2).

Groups Parameters	Group (1)(n=30)	Group (2)(n=30)	Group (3)(n=30)	Group (4)(n=30)	P
ALT (U/L)					
Range	16.00-21.00	23.00-37.00	45.00-58.00	65.00-78.00	<0.001
Mean +SD	18.15±1.63	29.15±4.26	53.35±3.44	71.35±4.04	
P1		0.008	0.001	0.001	
P2			0.021	0.003	
P3				0.008	
AST (U/L)					
Range Mean +SD	20.00-38.00	21.00-33.00	44.00-55.00	58.00-71.00	<0.001
	26.65±5.25	27.60±3.76	49.40±3.41	64.10±3.93	
GGT (U/L)					
Range	22.00-35.00	22.00-35.00	44.00-59.00	61.00-72.00	<0.001
Mean +SD	27.30±3.97	26.30±4.61	52.60±4.17	66.20±3.47	
P1		0.211	0.005	0.001	
P2			0.007	0.001	
P3				0.082	
Triglycerides (mg/dL)					
Range	115.00-134.00	133.00-150.00	190.00-211.00	217.00-234.00	<0.001

mean +SD	123.20±5.41	141.35±5.0	202.80±5.93	223.35±5.20	
P1		0.053	0.002	0.001	
P2			0.031	0.001	
P3				0.107	

Table (2): Comparison between groups regard to hepatic laboratory investigation

FABP1 levels were significantly higher in grades I, II, and III of pancreatic echogenicity than in grade 0. FABP1 levels, on the other hand, increased in grade III liver echogenicity significantly more than in grades I and II. Furthermore, FABP 1 levels increased significantly more in grades II, and III than in grades I. (Table 3).

Table (3): Comparison between groups regard to FABP 1, pancreatic echogenicity, and liver echogenicity

GroupsParameters	Group (1)(n=30)	Group (2)(n=30)	Group (3)(n=30)	Group (4)(n=30)	P value
FABP 1 (ng/mL)					
Range	19.00-28.00	24.00-39.00	25.00-39.00	30.00-48.00	<0.001
Mean +SD	23.25±3.02	30.25±4.23	32.70±4.11	40.75±4.87	
P1		0.036	0.035	0.011	
P2			0.126	0.022	
P3				0.047	
Pancreatic Echogenicity					
Grade 0	20 (100%)	13 (65%)	9 (45%)	6 (30%)	0.001
Grade 1	0 (0%)	7 (35%)	8 (40%)	11 (55%)	
Grade 2	0 (0%)	0 (0%)	3 (15%)	2 (10%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	1 (5%)	
P1		>0.05	0.011	0.003	
P2			>0.05	0.001	
P3				0.042	
Liver echogenicity					
Grade 0	20 (100%)	14 (70%)	10 (50%)	6 (30%)	
Grade 1	0 (0%)	6 (30%)	7 (35%)	11 (55%)	0.002

Grade 2 Grade 3	0 (0%) 0 (0%)	0 (0%) 0 (0%)	3 (15%) 0 (0%)	2 (10%) 1 (5%)	
P1		0.046	0.002	0.001	
P2			0.061	0.001	
P3				0.014	

Using FABP 1 as a predictor of pancreatic echogenicity, the sensitivity of FABP1 to diagnose pancreatic echogenicity was 86.0%, and specificity was 80.0% at a cut-off value of 32.0. The sensitivity was 81.0%, and the specificity was 76.0% when FABP1 was used as a diagnostic marker in liver echogenicity at a cut-off value of 31.0.

Table (4): Sensitivity, specificity, and accuracy of FABP 1 in prediction the of pancreatic echogenicity and liver echogeniciy

Area	Cut off value	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Pancreatic echogenicity				
0.821	32.0	0.001	0.610	0.832
Sensitivity Specificity Accuracy	86.0 80.0 84.0			
Liver echogenicity				
0.795	31.0	0.001	0.604	0.829

Discussion

Our findings show that there are no statistically significant differences between groups in terms of age or sex. According to Shi et al.(2012), there were no appreciable variations in age or gender between patients with obesity and those with normal weight (14). Similarly, Tirkes et al. (2019), concluded that patients with and without Type 2 DM and chronic pancreatitis had similar gender distributions (15).

According to Tariq and his colleagues, NAFPD prevalence increases with age. Fatty replacement in the pancreas was an inevitable aging process (8). This was also in line with a study's finding that the prevalence of fatty pancreas increased with age, with a positive correlation between age and NAFPD. Therefore, aging is considered an important risk factor for NAFPD. This might be related to Age-related metabolic dysfunction with associated prolonged dyslipidemia (16,17,18),19).

In contrast to earlier research (20), our study found no link between NAFPD and the male gender. Men were thought to have a higher chance of developing NAFPD because they deposited more visceral (abdominal) fat than women did, who accumulated more subcutaneous (gluteal and femoral) lipids (25,27).

In terms of blood glucose, there were statistically significant differences between groups, both fasting glucose and HbA1c showed a significant difference (high in group groups 2 and 4). Two earlier studies support our findings. The first was a study by Nakamura et al. (2017), who reported that HbA1c was significantly higher in the T2DM group compared with the non-DM group (21).

Additionally, Wu and Wang found that the fatty pancreas group had significantly higher FBG, PBG (postprandial blood glucose), and HbA1c values when compared to the normal pancreatic group (22). Furthermore, Della Corte et al. found that obese children complicated with NAFPD had higher insulin resistance and circulating levels of tumor necrosis factor-α and interleukin-1β than those without NAFPD (23). Similarly, a community cohort study held by Wong et al. also proved that adults with both NAFPD and NAFLD had a higher homeostasis model assessment of insulin resistance than those with either condition alone (24).

The current study showed that there was a significant statistical difference between groups concerning ALT, AST, and GGT. Regarding triglycerides(TG), there were substantial statistical differences between the groups. Shi et al. found that obese participants had higher BMI, waist circumference (WC), blood pressure, ALT, AST, TG, TC, LDL-c, and fasting glucose levels than normal-weight subjects, confirming our findings (14). Furthermore, Nakamura et al. concluded that there was a significant difference in the mean levels of AST, ALT, TG, and low-density lipoprotein (LDL) cholesterol between the two groups, with the T2DM group having considerably higher levels than the non-DM group (21). Wu and Wang, however, found that the fatty pancreas group had significantly higher mean total cholesterol, TG, and LDL-C values compared to the normal pancreas group (22).

In a previous trans-abdominal US study, it has been reported a correlation between fatty pancreas and liver enzymes including AST, ALT, and γGGT (25). In contrast, another study showed that no significant associations were found between fatty pancreas and AST, ALT, and γGGT levels (18).

Our data showed that as compared to the absence of a fatty pancreas, the presence of the disease was associated with significant values of BMI among groups. This result came in agreement with the study which showed that the proportions of subjects with central obesity and BMI>24 kg/m2 were significantly higher in the FP group than those in the non-FP group (18). Available studies have also reported an association between BMI and a fatty pancreas (25). An available study has reported that a fatty pancreas was associated with higher levels of total cholesterol, triglycerides, and high-density lipoprotein cholesterol than the control group (26).

In the present study, there were statistically significant associations between the NAFLD group and components of metabolic syndrome including aging, obesity, type 2 Diabetes mellitus (T2DM), and dyslipidemia. In agreement with our results, fatty liver was reported to be associated with insulin resistance, dyslipidemia, and obesity and is therefore considered a phenotype of metabolic syndrome(26).

The present study revealed significant associations of the fatty pancreas with aging, obesity, T2DM, and dyslipidemia and the association between NAFPD and NAFLD. Finally, Our findings indicated that NAFPD and NAFLD may have the same risk factors leading to fat accumulation in both organs such as obesity, dyslipidemia, and diabetes, so control of these risk factors decreases the incidence of both diseases.

In the past, the diagnosis of pancreatic steatosis was made on in vivo autopsy specimens. With the advent of more advanced and sophisticated imaging modalities, pancreatic steatosis is most often found using these imaging techniques. EUS is superior to the US in the detection of the fatty pancreas, especially in obese persons (8).

In the study in our hands, there was a significant statistical difference between groups concerning pancreatic echogenicity. There was a significant statistical difference between groups concerning liver echogenicity.

Lee et al. (2010) diagnosed an increased echogenicity of the pancreatic body over the kidney echogenicity during ultrasonography as a fatty pancreas. They found that insulin resistance, visceral fat, triglyceride, and alanine aminotransferase (ALT) tended to increase with the degree of fat deposition in the pancreas. They found the presence of a fatty pancreas along with fatty liver concurrently in many cases. They suggested that a fatty pancreas might be the initial indicator of "ectopic fat deposition" and an early marker of insulin resistance, which is a key element of fatty liver and/or metabolic syndrome (27).

Another study done by Al-Haddad et al. (2018) who used endoscopic ultrasound, also found hepatic steatosis, alcohol use, and increased BMI as predictors of pancreatic steatosis, with hepatic steatosis

being the strongest predictor with an odds ratio of nearly 14- fold. The US has some limitations considering that pancreas may not be well visualized in obese patients (28).

The fate of lipids is determined by intracellular lipid chaperones. These proteins, also known as fatty acid-binding proteins (FABPs), coordinate lipid trafficking and signaling in cells, and some isoforms are also strongly linked to metabolic and inflammatory pathways (32) To date, at least nine FABPs have been identified, each with its pattern of tissue expression. FABPs from the liver (L-), intestinal (I-), heart (H-), adipocyte (A-), epidermal (E-), ileal (Il-), brain (B-), myelin (M-), and testis (T-) are members of the family. Previous studies have demonstrated that FABP-1 acts a protective role in renal damage. It was hypothesized that pancreatic tissue with high FABP-1 levels would be protected against oxidative damage and inflammation (34).

Fatty Acid Binding protein 1 (FABP1) is a tissue-specific marker that can be used to diagnose NAFLD and NAFPD (11). According to Lu et al. (2020), a high FABP1 level was linked to overt NAFLD (after adjusting for age and sex) (30).

The present study showed that there was a significant statistical difference between groups concerning FABP 1. Positive significant correlation between FABP 1 and age and BMI, while there is a non-significant correlation between FABP 1 and female sex, systolic blood pressure, diastolic blood pressure, currently smoking, total cholesterol, triglycerides, HDL, LDL, GGT, AST, ALT, HbA1c and Leukocyte.

In our investigation, hyperechoic pancreas grades I, II, and III had considerably high FABP1 levels than grades 0 did. As opposed to grades I and II, grade III liver echogenicity shows a significant elevation in FABP1. Additionally, FABP 1 levels significantly increased in grades II, and III compared to grade I hepatic echogenicity.

The sensitivity, specificity, and overall accuracy of FABP1 to diagnose pancreatic echogenicity were reported to be 86.0%, 80.0%, and 84.0%, respectively, at the cut-off value of 32.0. The sensitivity, specificity, and overall accuracy of FABP1 as a diagnostic marker for hepatic echogenicity at a cutoff value of 31.0 were 81.0%, 76.0%, and 78.0%, respectively. In matching our findings, Lu et al. (2020) discovered that patients with overt NAFLD (grade 2 or 3) had a high serum FABP1 level that was considerably greater than that of patients with grade 1 NAFLD and healthy individuals.

Conclusion

Pancreatic steatosis, metabolic syndrome, and NAFLD all have a strong link. EUS is superior in the management of pancreatic steatosis and could have a significant impact on patient outcomes. FABP1 can be used to identify the non-alcoholic fatty pancreatic disease as a biomarker. Further studies are still needed to clarify this hot topic in gastroenterology.

Conflicts of interest: No conflicts of interest were encountered.

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