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Non Alcoholic Fatty Pancreatic Disease Significance, Importance and Risk factors

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Abstract: ***Background: Globally, diabetes mellitus (DM) is the third most common noncommunicable disease. Nonalcoholic fatty pancreas disease (NAFPD), is a disease characterized by pancreatic fat infiltration or pancreatic islet cell steatosis. The present work aimed to determine the prevalence of NAFPD among obese with and without DM, it is emerged as mirror image of NAFLD because of the same embryological origin. Evaluation of associated risk factors. Methods: This was cross sectional study among conducted on (200) subjects. The study protocol was presented to the ethical committee of Al-azhar faculty of medicine for approval. All subjects were subjected to the following: History, clinical examination and laboratory investigations including (Serum Insulin level, HOMA-IR and Fatty Acid Binding protein1 (FABP1). Imaging: (Abdominal Ultrasound and EUS). Results: Prevalence of NAFPD was 37% among all of the studied sample.There was a significant relationship between NAFPD and T2DM. Mean value of BMI, Hb A1C and HOMA IR were statistically higher among Cases with NAFPD than Cases without NAFPD. There were statistically significant positive correlation between Fatty Acid Binding Protein I (F ABPI) and BMI. Conclusion: There is a significant association between the presence of nonalcoholic fatty pancreas disease and diabetes mellitus. Positive statistically significant correlation between insulin resistance and NAFLD. Positive correlations between plasma FABP1 levels and (BMI and HbA1c). FABP1 has a good diagnostic value in nonalcoholic fatty pancreas disease cases.***

Keywords: Diabetes mellitus- Nonalcoholic fatty pancreas disease- prevalence

1. Introduction

Globally, diabetes mellitus (DM) is the third most common noncommunicable disease, after cardiovascular diseases and cancer. The World Health Organization (WHO) showed that there were 371 million DM patients in the world in 2012. Changes in dietary patterns and lifestyles have made diabetes one of the major public health problems in China. Pancreatic β-cell dysfunction and insulin resistance are 2 key links in the pathogenesis of diabetes, and their occurrence is closely related to the ectopic deposition of pancreatic lipids[1; 2].

Pancreatic fat ectopic deposition disease, also known as nonalcoholic fatty pancreas disease (NAFPD), is a disease characterized by pancreatic fat infiltration or pancreatic islet cell steatosis. NAFPD is an independent risk factor for the pathogenesis of type 2 diabetes mellitus (T2DM) and impaired glucose regulation (IGR). But its etiology has not yet been determined. Animal and clinical studies have shown that a high-fat diet could cause NAFPD, resulting in impaired β-cell function, decreased insulin secretion, insulin resistance, and abnormal adipokine secretion. Also, patients with NAFPD have an increased risk of developing T2DM [3].

Studies concerning NAFPD, so far, have investigated different stages of glucose metabolism (prediabetes and diabetes) to find associations between the diseases. [4]

Fatty acid-binding proteins (FABPs) are a family of 15-kDa proteins. Nine different FABPs have been identified and named according to the tissues in which they are found. FABP1 (also known as liver-type fatty acid-binding protein or LFABP) is expressed mainly in the liver, but small quantities are also found in the kidneys and small intestine. Previous studies on different types of FABPs have shown that these proteins are associated with tissue damage, including myocardial injury and damage to other organs such as the liver, kidneys, intestine and lungs [5; 6].

FABP1 is a 14-kDa protein which is expressed in the hepatocytes and the proximal tubular cells of the kidneys, and participates in fatty acid metabolism in the cytoplasm. Furthermore, FABP1 facilitates the transportation, storage, and utilization of fatty acids and their acyl-CoA derivatives and may exert a protective effect against lipotoxicity by facilitating their oxidation or incorporation into TGs and binding otherwise cytotoxic-free fatty acids [7]. Some studies on chronic hepatitis C, NASH, and NAFLD have shown that serum FABP1 may be a new diagnostic marker to detect liver injury [8; 9].

The present work aimed to determine the prevalence of NAFPD among obese with and without DM, it is emerged as mirror image of NAFLD because of the same embryological origin. Evaluation of associated risk factors.

2. Patients and Methods

This was cross sectional study among conducted on (200) subjects.Informed written consents was taken from all participants in this study after explaining the aim for

them.The study protocol was presented to the ethical committee of Al-azhar faculty of medicine for approval**.**

Four groups of patients was included;

1) Group 1 Normal BMI, Non-diabetics
2) Group 2 Normal BMI, Diabetics or with impaired fasting blood sugar
3) Group 3 BMI over 25, Non-diabetics
4) Group 4 BMI over 25, Diabetics or with impaired fasting blood sugar

Inclusion Criteria: Normal and obese peoples with and without DM type 2. Both sexes were included.All subjects aged from 18-70 years old.Subjects fulfill criteria of metabolic syndrome

Exclusion Criteria: Patients with history of chronic pancreatitis or previous attacks of pancreatitis and admission to the hospital. Drugs induced pancreatitis' (Amiodarone, cortisone, Valproate, methotrexate). Alcohol intake > 20gm/day. Patients with liver diseases other than NAFLD.

All subjects were subjected to the following:

A) Full history taking and thorough clinical examination: including measurement of arterial blood pressure and calculation of the body mass index (BMI).

B) Laboratory investigations including:

- Complete blood count (CBC, ESR).
- Fasting blood sugar.
- Liver function tests including alanine amino transferase, aspartate amino transferase, gamma glutamyltranspeptidase, alkaline phosphatase (ALT, AST, GGT, ALP) serum bilirubin, serum albumin, HBsAg and HCVAb
- Lipid profile including (cholesterol, triglycerides, HDL, and LDL).
- Serum Insulin level for calculating insulin resistance (IR).
- HOMA-IR
  Was assessed using the given mathematical equation; HOMA-IR = fasting insulin (mU/ml) fasting plasma glucose (mmol/l)/22.5 **[(10)].** A HOMA value of 2.18 signifies IR.
- Fatty Acid Binding protein1 (FABP1)FABP was evaluated by the enzyme-linked immunosorbent assay (ELISA) according to **Haltern et al. [(11)]**and the deviation from the normal was correlated with other investigations and clinical manifestations of the subjects.

C) Imaging:

Abdominal Ultrasound

Was done for grading of fatty liver and pancreas by radiologist or gastroenterologist. Fatty liver was diagnosed as follows [(12)]:

- Level 0, normal liver echogenicity
- Level 1, a slight increase in liver echogenicity with no attenuation in the far field
- Level 2, a moderate increase in liver echogenicity with light attenuation in the far field and the diaphragm and vessels clearly visible
- Level 3, a substantial increase in liver echogenicity with poor visualization of the diaphragm and the vessels.
- NAFLD was diagnosed when the liver appeared as level1 to 3.

The pancreas echogenicity was also classified into 4 grades [(13)]**:**

- Level 0, the pancreas echogenicity was similar to the kidney parenchymal
- Level 1, pancreas echogenicity was slightly higher than in the kidney if the operator can see both in the same view in the transverse epigastric scan with slight move to the right, if the pancreas and kidney could not be displayed in the same screen, the radiologist compared the kidney with the liver and then compared the liver with the pancreas
- Level 2, a substantial increase in pancreas echogenicity but lower than the retroperitoneal fat echogenicity
- Level 3, the pancreas echogenicity was similar to or higher than the retroperitoneal fat.
  NAFPD was diagnosed when the pancreas appeared as level 1-3.

EUS:

The classification system was adapted from that used by **Marks et al. [(13)]** and **Worthen and Beabeau[(14)].** In addition to assessment of pancreatic echogenicity, we also assessed the pancreas for clarity of the parenchyma and pancreatic duct margins.

- Grade I is defined as pancreas in which 80% of the parenchyma was hypoechoic or isoechoic when compared with the spleen, the main pancreatic duct was clearly delineated, and fine, "salt and pepper" dots in the pancreatic parenchyma were clearly seen.
- Grade II was defined as pancreas in which 80% of the parenchyma was hyperechoic when compared with the spleen, the main pancreatic duct was clearly delineated, and fine, salt and pepper dots in the pancreatic parenchyma were clearly seen.
- Grade III was defined as pancreas in which 80% of the parenchyma was moderately more hyper-echoic as compared with the spleen, the main pancreatic duct margins were moderately obscured, and fine, salt and pepper dots in the pancreatic parenchyma were moderately blurry.
- Grade IV was defined as pancreas in which 80% of the parenchyma was severely more hyperechoic when compared with the spleen, the pancreas could not be separated from the adjacent fat, the main pancreatic duct margins were severely obscured, and fine, salt and pepper dots in the pancreatic parenchyma were severely obscured.

Statistical Analysis: Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 24. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were

compared using Chi square test and fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) tests were used to verify assumptions for use in parametric tests. To compare continuous quantitative data of two groups, Mann whitney test (for non-normally distributed data) and independent sample t test (for normally distributed data) were used. The level statistical significance was set at 5% (P<0.05).

3. Results

There was no statistically significant difference between studied groups regarding Age and Sex **(Table 1)**.

There were statistically significant decrease in HOMA IR among Group 1 than Group 2, Group 3 and Group 4.There were statistically significant decrease in HOMA IR among Group 2 than Group 3 and Group 4.There were statistically significant decrease in HOMA IR among Group 3 than Group 4.There were statistically significant decrease in F Acid Binding Protein I (F ABPI) among Group 1 than Group 2, Group 3 and Group 4.There were statistically significant decrease in F Acid Binding Protein I (F ABPI) among Group 2 than Group 3 and Group 4.There were statistically significant decrease in F Acid Binding Protein I (F ABPI) among Group 3 than Group 4 **(Table 2)**.

There was statistically significant difference between studied groups regarding NAFPD **(Table 3)**.

Table (4) shows that there were statistically significant positive correlation between F Acid Binding Protein I (F ABPI) and BMI, Fasting Bl. Sugar, Hb A1c, S. Triglecride, LDL, ESR, ALT, AST, F. Insulin level and HOMA IR, there were statistically significant negative correlation between F Acid Binding Protein I (F ABPI) and HDL, while there was no statistically significant difference between F Acid Binding Protein I (F ABPI) and other numerical data.

This table shows that Distribution of NAFPD, Cases with NAFPD was 74 (37%) and Cases without NAFPD was 126 (63%) **(Table 5).**

Mean value of BMI was statistically higher among Cases with NAFPD than Cases without NAFPD (27.48, 23.63) p value= 0.000There was statistically significant difference between Cases with NAFPD and Cases without NAFPD regarding Hb A1c **(Table 6)**.

Mean value of HOMA IR was statistically higher among Cases with NAFPD than Cases without NAFPD (5.15, 1.93) p value= 0.000Mean value of F Acid Binding Protein I (F ABPI) was statistically higher among Cases with NAFPD than Cases without NAFPD (34.63, 22.53) p value= 0.000 **(Table 7).**

This table shows that regarding diagnostic accuracy of F Acid Binding Protein I (F ABPI) in detection of NAFPD Sensitivity was 70.3%, Specificity was 77%, PPV was 64.2% and NPV was 81.5%, accuracy 74.5% **(Table 8).**

Table 1: Comparison between studied groups regarding demographic data

			Group 1	Group 2	Group 3	Group 4	F. test	P. value
Age	Rang		19 - 66	19 - 66	19 - 69	19 - 69	.384	0.765
	Mean ± SD		39.58 ± 14.83	39.98 ±14.89	42.00 ± 13.83	42.00 ± 15.41		
Sex	female	No.	30	33	25	29	X^2 2.698	0.441
		%	60.0%	66.0%	50.0%	58.0%		
	male	No.	20	17	25	21		
		%	40.0%	34.0%	50.0%	42.0%		

Table 2: Comparison between studied groups regarding HOMA IR and Protein I (F ABPI)

		Group 1	Group 2	Group 3	Group 4	F.test	P. value	LSD
HOMA IR	**Rang**	0.20 - 2.30	1.10 - 5.50	0.20 - 6.40	0.30 - 8.70	45.024	0.000	P1= 0.001 P2= 0.000 P3= 0.000 P4= 0.001 P5= 0.000 P6= 0.000
	Mean ± SD	1.52 ± 0.36	2.51 ± 0.99	3.53 ± 1.58	4.94 ± 2.44			
F Acid Binding Protein I (F ABPI)	**Rang**	6.80 - 26.60	6.90 - 46.50	20.2 - 46.50	23.40 - 56.70	110.980	0.000	P1= 0.018 P2= 0.000 P3= 0.000 P4= 0.000 P5= 0.000 P6= 0.000
	Mean ± SD	15.69 ± 5.79	19.45 ± 8.92	31.42 ± 7.07	41.49 ± 9.27			

P1--→ between Group 1 and Group 2 . P2-→ between Group 1 and Group 3. P3-→ between Group 1 and Group 4 .P4-→ between Group 2 and Group 3 . P5-→ between Group 2 and Group 4
P6-→ between Group 3 and Group 4

Table 3: Comparison between studied groups regarding NAFPD

			Group 1	Group 2	Group 3	Group 4	t.test	P. value
NAFPD	No	No.	50	43	21	12	66.32	.000
		%	100.0%	86.0%	42.0%	24.0%		
	Yes	No.	0	7	29	38		
		%	.0%	14.0%	58.0%	76.0%		

Table 4: Correlation between F Acid Binding Protein I (F ABPI)and other numerical variables

Correlation	Pearson's correlation	
	r	p
Age * F Acid Binding Protein I (F ABPI)	.087	0.222
BMI * F Acid Binding Protein I (F ABPI)	.619	0.000
Fasting Bl. Sugar * F Acid Binding Protein I (F ABPI)	.297	0.000
Hb A1c * F Acid Binding Protein I (F ABPI)	.255	0.000
S. cholestrol * F Acid Binding Protein I (F ABPI)	.115	0.106
S. Triglecride * F Acid Binding Protein I (F ABPI)	.559	0.000
LDL * F Acid Binding Protein I (F ABPI)	.226	0.001
HDL * F Acid Binding Protein I (F ABPI)	-.171-	0.016
Hb * F Acid Binding Protein I (F ABPI)	.009	0.897
Platelet * F Acid Binding Protein I (F ABPI)	-.027-	0.705
WBC * F Acid Binding Protein I (F ABPI)	-.010-	0.889
ESR * F Acid Binding Protein I (F ABPI)	.429	0.000
ALT * F Acid Binding Protein I (F ABPI)	.255	0.000
AST * F Acid Binding Protein I (F ABPI)	.351	0.000
GGT * F Acid Binding Protein I (F ABPI)	.132	0.063
ALP * F Acid Binding Protein I (F ABPI)	.073	0.304
S. billrubin * F Acid Binding Protein I (F ABPI)	-.009-	0.902
S.Albumin * F Acid Binding Protein I (F ABPI)	-.036-	0.614
F.Insulin level * F Acid Binding Protein I (F ABPI)	.457	0.000
HOMA IR * F Acid Binding Protein I (F ABPI)	.502	0.000

Table 5: Distribution of NAFPD among all the studied groups

	No.	%
Cases with NAFPD	74	37.0
Cases without NAFPD	126	63.0

Table 6: Comparison between Cases with NAFPD and Cases without NAFPD regarding BMI and Hb A1c

		Cases with NAFPD	Cases without NAFPD	t. test	P. value
BMI	Mean ± SD	27.48± 2.79	23.63±3.57	7.924	.000
Hb A1c	Mean ± SD	6.31± 1.40	5.98±1.35	1.671	.04

Table 7: Comparison between Cases with NAFPD and Cases without NAFPD regarding HOMA IR and F Acid Binding Protein I (F ABPI)

		Cases with NAFPD	Cases without NAFPD	t. test	P. value
HOMA IR	Mean ± SD	5.15± 1.71	1.93±.850	17.698	.000
F Acid Binding Protein I (F ABPI)	Mean ± SD	34.63± 11.35	22.53±11.55	7.199	.000

Table 8: Diagnostic accuracy of F Acid Binding Protein I (F ABPI) in detection of NAFPD

	Cut off value	AUC	Sensitivity%	Specificity%	PPV%	NPV%	accuracy
F Acid Binding Protein I (F ABPI)	29.5	0.78	70.3%	77%	64.2%	81.5%	74.5%

4. Discussion

In the current study, regarding prevalence of NAFPD, Cases with NAFPD was 74 (37%) and Cases without NAFPD was 126 (63%). Percentage of NAFPD was higher among Group 4 BMI over 25, Diabetics or with impaired fasting blood sugar followed by Group 3 BMI over 25, Non-diabetics and Group 2 Normal BMI, Diabetics or with impaired fasting blood sugar.

In the current study, regarding prevalence of NAFPD, Cases with NAFPD was (37%). These findings were comparable with the result of study made by **Lesmanaet al.,** [15] who found fatty pancreas was present in 315 (35.0 %) patients. Fatty pancreas is a common finding during medical check-up with a prevalence of 35 %.

Recent meta-analysis also showed that there was a significant relationship between NAFPD and T2DM (RR 2.08; 95%CI=1.44-3; p <0.001) [16].

A recent study involving 8097 subjects underwent health check-up in Taiwan found only 16 % prevalence of fatty pancreas detected by abdominal ultrasound. [17].

In Indonesia, which represents the biggest Southeast Asian country, the prevalence of NAFPD in the medical check-up population was 35%. Previous studies had shown that NAFPD is associated with T2DM [18; 15].

In this study, mean value of BMI was statistically higher among Cases with NAFPD than Cases without NAFPD (27.48, 23.63) p value= 0.000This was in agreement with**Weng et al.,** [(3)]who found BMI, in the NAFPD group were higher than in the without NAFPD group.

In this study, mean value of Hb A1C were statistically higher among Cases with NAFPD than Cases without NAFPD.This was in agreement with**Lesmanaet al.,** [(15)]who revealed there is a significant association between the presence of fatty pancreas and diabetes mellitus.

This study showed that, mean value of HOMA IR was statistically higher among Cases with NAFPD than Cases without NAFPD (5.15, 1.93) p value= 0.000

This was in agreement with **Weng et al.,** [(3)]who found BMI, HOMA-IR were higher than in the without NAFPD group. This study showed that, there were statistically significant positive correlation between Fatty Acid Binding Protein I (F ABPI) and BMI.In harmony with **Lu et al.,** [(19)]who showed positive correlations between plasma FABP1 levels and BMI.

In agreement with **Shi et al.** [(20)] reported marked increases in FABP1 in healthy obese subjects compared to normal-weight subjects, and that this was strongly correlated with central adiposity.

Elevation of serum FABP1 in obese subjects may be compensatory up-regulation to counteract the metabolic stress imposed by obesity. In addition, it is possible that obesity may cause resistance to the action of FABP1 leading to its compensatory up-regulation. [(19)]**.**

This study showed that, there were statistically significant positive correlation between Fatty Acid Binding Protein I (F ABPI) and HOMA IR. In agreement with **Shi et al.** [(20)] reported that serum FABP1 was positively correlated with insulin resistance in humans.

5. Conclusion

It can be concluded that there is a significant association between the presence of nonalcoholic fatty pancreas disease and diabetes mellitus. BMI were higher in NAFLD group than in without NAFPD group. Positive statistically significant correlation between insulin resistance and NAFLD. Positive correlations between plasma FABP1 levels and BMI. There was a significant positive correlation between FABP1 and HbA1c. FABP1 has a good diagnostic value in nonalcoholic fatty pancreas disease cases.

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