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Abdel-Rahman Mahrous
abdelrahmanmahrous334@gmail.com

Mohammed Noshy Al-Alfy
Internal Medicine, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Mohammed Abdel-Hassib
Internal Medicine, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Mohammed A. Amin
Diagnostic and Interventional Radiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

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ORIGINAL ARTICLE

Non-alcoholic Pancreatic Lipomatosis among the Egyptian type 2 Diabetic Patients

Abdelrahman M. Mohammed [a,*], Mohammed N. Al-Alfy [a], Mohammed Abdel-Hassib [a], Mohammed A. Amin [b]

[a] Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[b] Department of Diagnostic and Interventional Radiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Obesity has become a serious public health problem globally. Non-alcoholic pancreatic lipomatosis is characterized by pancreatic fat infiltration or pancreatic islet steatosis resulting in abnormal adipokine secretion, insulin resistance, impaired βcell function, and decreased insulin secretion.***

Aim: ***To assess the relationship between non-alcoholic fatty pancreatic disease and type 2 diabetes mellitus among Egyptian patients.***

Methods: ***We enrolled 80 type 2 diabetic patients along with 80 healthy control individuals, all were assessed by abdominal ultrasound and CT scan to determine the degree of pancreatic steatosis based on echogenicity of pancreatic tissue, and four-scale grading system as the visual assessment criteria for pancreatic fat deposition using CT images.***

Results: ***We found that the diabetic group demonstrated a prevalence of fatty pancreas accounting for 43.8% versus 7.5% in the healthy control group with a p-value <0.001. BMI, ALT, AST, amylase, lipase, ALT, AST, cholesterol, LDL, TG, and HbA1c were positively correlated with the degree of fatty pancreas. BMI, TG, and LDL levels are independent predictors for fatty pancreas after adjusting for other risk factors such as cholesterol level, HDL, and HBA1c with p values <0.01. BMI, ALT, AST, Hb A1c, and lipid profile can significantly predict a fatty pancreas.***

Conclusion: ***Pancreatic steatosis is significantly associated with type 2 diabetes, glycemic control, lipid profile, and body mass index. The degree of non-alcoholic pancreatic lipomatosis by CT scan significantly correlates with body mass index, lipid profile, and glycemic control.***

Keywords: Non-alcoholic pancreatic lipomatosis, type 2 diabetes, obesity

1. Introduction

Type 2 diabetes mellitus (T2D) has been more common and more commonplace in recent decades, coinciding with a global upsurge in obesity rates. Adipose tissue biology has recently attracted a lot of attention due to the link between type 2 diabetes and obesity. [1]

Over time, the understanding of adipose tissue has evolved, and it is now recognized as more than just a passive storage site for fat. On the contrary, it is recognized as an endocrine organ that is metabolically active and capable of releasing a wide variety of hormones and other compounds with biological activity.[2, 3]

Lipid droplet accumulation inside cells can lead to cellular malfunction and cell death, a condition called lipotoxicity .[4,5] In addition, research has shown that skeletal tissue and liver cell lipid levels, rather than blood free fatty acid levels, are the most important factors in insulin resistance .[6,7]

The link between metabolic syndrome and type 2 diabetes, as well as metabolic fatty liver disease (MFLD), which causes ectopic fat accumulation in the liver, has been the subject of substantial research. The clinical significance of ectopic fat deposition in other organs, especially the pancreas, has, however, received little attention in the scientific community until lately.[6,8,9]

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* Corresponding author at: Internal Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt.
E-mail address: abdelrahmanmahrous334@gmail.com (A. M. Mohammed).

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Pancreatic fat accumulation can occur in non-obese individuals owing to several other causes, such as prolonged alcohol consumption, viral infections, chemotherapy, and cystic fibrosis. Pancreatic fat buildup occurs when adipocytes infiltrate the lobules or interlobular spaces or when lipid droplets are inside the cells.[10]

Many people have different opinions on whether or not type 2 diabetes and non-alcoholic fatty pancreatic disease are related. Multiple studies have shown that pancreatic adiposity is more common in people with type 2 diabetes than in people without the disease.[11,12,13,14]

However, other studies have observed no difference in pancreatic fat accumulation between the two groups .[15,16,17]

Thus, we conducted a case-control study to assess the relationship between non-alcoholic fatty pancreatic disease and type 2 diabetes mellitus among Egyptian patients.

2. Patients and methods

Eighty adults with type 2 diabetes and eighty healthy controls were included in the study. We used a four-point scale to visually evaluate the amount of pancreatic fat deposition in CT images, and an abdominal ultrasound to measure the degree of pancreatic steatosis according to the echogenicity of pancreatic tissue.

This study did not include people who were previously diagnosed with type 1 diabetes, pancreatitis, malnutrition, alcoholism, or who were using amiodarone, corticosteroids, valproate, or methotrexate.

Every single participant in the study had to undergo a battery of tests, including taking their medical history, having their blood pressure, height, and weight taken, as well as having their lipid profiles (total cholesterol, triglycerides, HDL, LDL, serum amylase, and lipase) and liver function tests (ALT, AST, direct and indirect serum bilirubin, serum albumin, and liver function tests) performed.

Abdominal CT scans without contrast were used to evaluate the degree of fatty pancreas based on a four-scale grading system; ultrasound was used to examine the pancreas' echogenicity in comparison to the kidney: Fat substitution in the head area is a hallmark of type 1A. Type 1B is defined by the replacement of the body, neck, and head with adipose tissue. Substituting fat for the uncinate process and the head is what distinguishes type 2A. Nearly full pancreatic replacement, with the exception of the peri-biliary area, characterizes type 2B.

2.1.Ethical considerations: All patients signed a written informed consent before participation, all procedures in this study followed AL-Azhar University Ethical Committee Regulations, and ethical approval was obtained in 2020.

2.1.Statistical analysis: Statistical analysis was conducted using SPSS 27th edition; categorical variables were presented in count and percent, and the Pearson Chi2 test was compared between study groups. Quantitative variables were presented in mean, standard deviation, minimum, and maximum; comparison between study groups was conducted using the Whitney U test after normality testing using the Wilk test. Spearman correlation test was conducted to assess the relation between laboratory findings and degree of fatty pancreas by CT scan. A multivariate linear logistic regression model was conducted to determine predictors for the degree of fatty pancreas by CT of the demographics and laboratory findings; all variables with significant correlation <0.05 were included in the model. All tests were two-sided, and p values <0.05 were considered significant.

3. Results

Eighty people with diabetes who had been diagnosed according to ADA standards were included in the study, along with eighty healthy controls. According to table 1, no statistically significant difference was found in age, gender, or body mass index (BMI) between the study groups, as indicated by p values > 0.05. There was a significant difference in C-reactive protein levels between the diabetes and control groups ($p < 0.001$). Compared to the control groups, the diabetes groups had significantly higher levels of lipase, AST, and ALT ($p = 0.032$, <0.001, and <0.001 correspondingly). In comparison to the control group, the diabetic group had considerably higher levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL), as well as significantly lower levels of high-density lipoprotein (HDL), all with p values less than 0.001. The HbA1c level was noticeably greater in the diabetes group when contrasted with the control group (p value <0.001). There were no statistically significant differences between the research groups for Amylase and Albumin, with p values greater than 0.05.

The prevalence of fatty pancreas was 43.8% in the diabetes group and 7.5% in the healthy control group, with a p value of less than 0.001. In the group of diabetics, computed tomography revealed that 3.8% were in the 1a stage, 15% in the 1b stage, 15% in the 2a stage, and 18.8% in the 2b stage, in contrast to 2.5% in the control groups and 5% in the 2b groups, with p values less than 0.001.

Table 1. Comparison of demographic characteristics between study groups.

		GROUP				
		Control		Diabetic		
		Mean± SD	Min-Max	Mean± SD	Min-Max	P value
AGE (YEARS)		50.9±9.4	32-72	51.3±9.4	32-72	0.808
BMI (KG/M²)		25.7±4.2	20-42	28.8±7.8	18-43	0.246
		Count	%	Count	%	
GENDER	Female	42	52.5%	46	57.5%	0.525
	Male	38	47.5%	34	42.5%	
		Mean± SD	Min-Max	Mean± SD	Min-Max	P value
ESR (FIRST HOUR)		19.2±5.6	11-29	.±.		NA
CRP (MG/DL)		0.7±0.14	0.4-1	10.41±16.21	0.4-67	<0.001
AMYLASE (MG/DL)		53.5±12.4	35-82	57.4±16.3	35-100	0.229
LIPASE (MG/DL)		48.6±35.5	1-120	67.2±48.2	1-170	0.032
ALT (IU)		19±8.9	5-34	44.8±38.3	5-160	<0.001
AST (IU)		20.9±5.9	14-35	40.8±31.2	15-140	<0.001
BILI TOTAL (MG/DL)		0.82±0.28	0.4-1.2	.±.		NA
BILI DIRECT (MG/DL)		0.2±0.08	0.1-0.3	.±.		NA
ALBUMIN (GM/DL)		4.14±0.5	3.5-5.1	4.1±0.49	3-5	0.700
CHOLESTEROL (MG/DL)		185.9±27.9	155-289	220.8±47.4	155-310	<0.001
TG (MG/DL)		137.2±24.2	105-220	166.1±41	112-250	<0.001
HDL (MG/DL)		46±9.9	21-65	39.4±12.3	21-62	<0.001
LDL (MG/DL)		99.7±33.7	70-190	126.1±46.4	75-190	<0.001
FBS (MG/DL)		92±10.3	75-115	.±.		NA
2HPP (MG/DL)		128.9±14	95-182	.±.		NA
HBA1C (%)		5.62±0.27	5.2-6.2	7.29±0.76	6.4-10	<0.0001
		Count	%	Count	%	P value
US	Hyperechoic parenchyma	6	7.5%	35	43.8%	<0.001
	Normal pancreas	74	92.5%	45	56.3%	
CT	1a	0	0.0%	3	3.8%	<0.001
	1b	2	2.5%	5	6.3%	
	2a	0	0.0%	12	15.0%	
	2b	4	5.0%	15	18.8%	
	Normal Pancreas	74	92.5%	45	56.3%	

BMI, ALT, AST, amylase, lipase, cholesterol, LDL, TG and HbA1c were positively correlated with degree of fatty pancreas with rho=0.834, 0.625, 0.459, 0.537, 0.629, 0.672, 0.494, and 0.432 respectively and p values <0.01. while HDL was negatively correlated with degree of fatty pancreas with rho= -0.383, and p value 0.013.

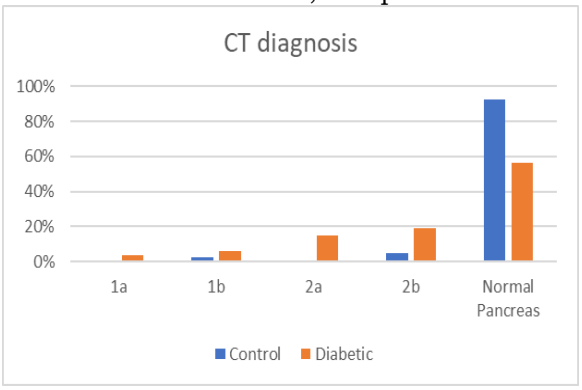


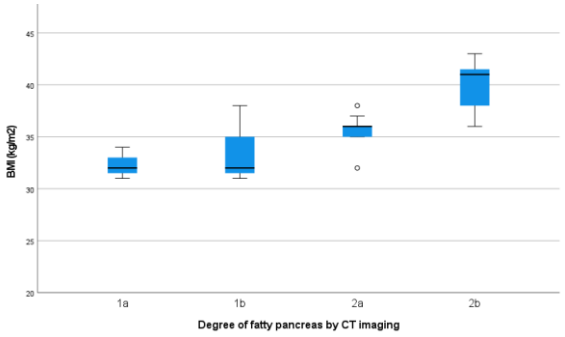
Figure 1. Bar chart showing degree of fatty pancreas between groups.

Table 2. Correlation matrix between degree of fatty pancreas by CT diagnosis with laboratory findings.

	CT DIAGNOSIS	
	Rho	P value
AGE (YEARS)	0.275	0.081
BMI (KG/M²)	0.834**	<0.001
CRP (MG/DL)	0.625**	<0.001
AMYLASE (MG/DL)	0.459**	0.003
LIPASE (MG/DL)	0.537**	<0.001
ALT (IU)	0.629**	<0.001
AST (IU)	0.672**	<0.001
ALBUMIN (GM/DL)	0.072	0.654
CHOLESTEROL (MG/DL)	0.575**	<0.001
TG (MG/DL)	0.518**	0.001

HDL (MG/DL)	-0.383*	0.013
LDL (MG/DL)	0.494**	0.001
HBA1C (%)	0.432**	0.005

BMI, TG, and LDL levels are independent predictors for fatty pancreas after adjusting for other risk factors such as cholesterol level, HDL, and HBA1c with p values <0.01.



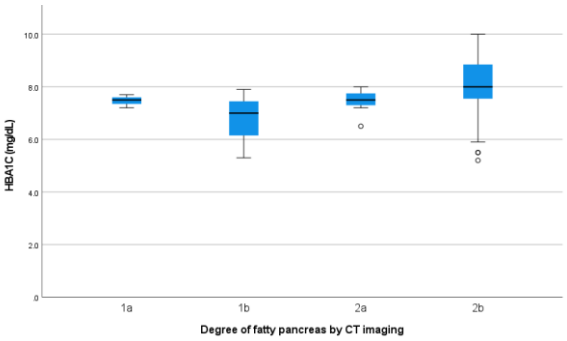


Figure 2. Box plot showing BMI and HbA1c according to degree of fatty pancreas by CT imaging.

Table 3. Linear regression model for predictors of fatty pancreas.

	UN-STANDARDIZED COEFFICIENTS		STANDARDIZED COEFFICIENTS			95% CONFIDENCE INTERVAL	
	B	Std. Error	Beta	T	P value	Lower Bound	Upper Bound
(CONSTANT)	6.347	0.517		12.277	<0.001	5.325	7.368
BMI (KG/M²)	0.06	0.013	0.405	4.464	<0.001	0.033	0.086
CHOLESTEROL (MG/DL)	-0.001	0.003	-0.051	-0.345	0.731	-0.008	0.005
TG (MG/DL)	-0.02	0.004	-0.773	-5.175	<0.001	-0.028	-0.012
HDL (MG/DL)	0.008	0.006	0.1	1.402	0.163	-0.003	0.02
LDL (MG/DL)	-0.007	0.002	-0.316	-2.97	0.003	-0.012	-0.002
HBA1C (%)	0.039	0.055	0.042	0.712	0.477	-0.069	0.148
A DEPENDENT VARIABLE: CT DIAGNOSIS							

BMI, ALT, AST and Hb A1c can significantly predict fatty pancreas using cutoff point 30 kg/m2, 33 IU, 32 IU and 7 %, with sensitivity 95%, 68.3%, 70.7%, 80.5%, and specificity 100%, 99.0%, 92.0%, and 97.5% respectively.

Lipid profile can significantly predict fatty pancreas using cutoff point 220 mg/dl of cholesterol, 175 mg/dl of TG <33.5 mg/dl of HDL, and 160 mg/dl of LDL, with sensitivity 100%, and specificity 99-96% respectively.

Table 4. ROC analysis showing predictability of BMI, liver transaminases and glycated hemoglobin for fatty pancreas.

	AUC	P VALUE	95% CONFIDENCE INTERVAL	CUT OFF	SENSITIVITY	SPECIFICITY
BMI (KG/M²)	0.951	<0.001	0.885-1	30	95%	100%
ALT (IU)	0.786	<0.001	0.68-0.89	33	68.3%	99.0%
AST (IU)	0.837	<0.001	0.75-0.92	32	70.7%	92.0%
HBA1C (%)	0.874	<0.001	0.789-0.96	7	80.5%	97.5%
CHOLESTEROL (MG/DL)	1	<0.001	1-1	>220	100%	99%
TG (MG/DL)	1	<0.001	0.999-1	>175	100%	99%
HDL (MG/DL)	0.004	<0.001	0-0.013	<33.5	100%	99%
LDL (MG/DL)	0.981	<0.001	0.961-1	>160	100%	96%

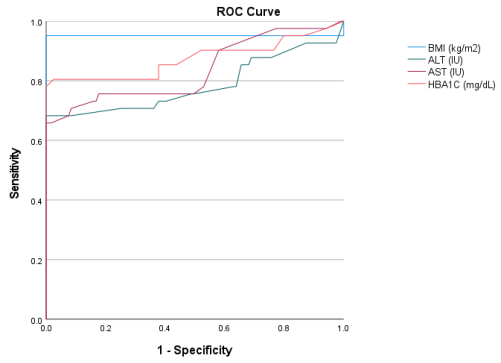


Figure 3. ROC curve showing predictability of BMI, liver transaminases and glycated hemoglobin for fatty pancreas.

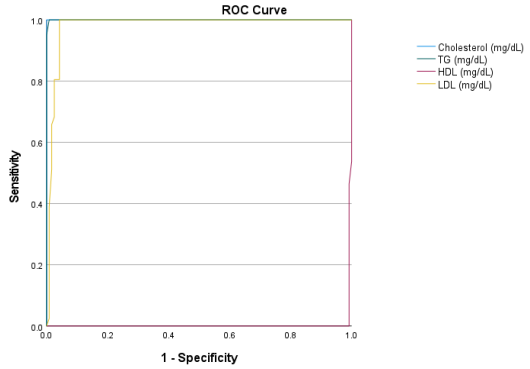


Figure 4. ROC curve showing predictability of lipid profile for fatty pancreas.

4. Discussion

Pancreatic adipose tissue that is not caused by alcoholic liver disease, viral infections, pollutants, or inherited metabolic disorders is called nonalcoholic fatty pancreas disease (NAFPD).[18] Rather, it is associated with insulin resistance, obesity, metabolic syndrome, poor diet, or getting older. [19]

Concurrent with the epidemic of obesity that has gripped the globe in the last several decades has come a dramatic increase in the incidence and prevalence of type 2 diabetes mellitus (T2D).[10]

The prevalence of obesity has led to a significant increase in the occurrence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic fatty pancreas disease (NAFPD) across all age groups .[20] In adults, the prevalence of fatty pancreas is around 27%, ranging from 16% to 35%. A strong and consistent correlation exists between NAFPD and obesity .[21, 22]

We conducted a case-control study to assess the association between Nonalcoholic pancreatic lipomatosis (NAPL) and (T2D); we found that the diabetic group demonstrated a prevalence of fatty pancreas, accounting for 43.8% versus 7.5% in the healthy control group, with p-value <0.001. In the diabetic group, CT showed that 1a stage accounted for 3.8%, stage 1b 15%, stage 2a 15%, and stage 2b in 18.8% compared to 2.5% of stage 1b and 5% of stage 2b in the control groups with p values <0.001.

Beta cell dysfunction and pancreatic adipose tissue buildup, which contribute to type 2 diabetes, was initially documented by Tushuizen et al. Type 2 diabetics had a higher median pancreatic fat percentage (20.4% vs. 9.7%, P = 0.032) than age- and BMI-matched controls. However, unlike type 2 diabetes patients, non-diabetics showed a significant association between pancreatic adipose tissue and beta cell dysfunction .[14]

People with NAFLD were more likely to develop prediabetes or diabetes, according to 2013 cross-sectional study by Ou et al. [odds ratio (OR) = 1.798, 95%CI: 1.544-2.094] and diabetes (OR = 2.578, 95%CI: 2.024-3.284), respectively. Fatty pancreas was associated with an increased risk of diabetes (1.379; 95%CI: 1.047-1.816) and prediabetes (1.221; 95%CI: 1.002-1.491), particularly in males..[13]

Similarly, research conducted by Pacifico et al. on obese adolescents with NAFLD found that patients with prediabetes had a considerably larger amount of fat in their pancreas (3.60%) compared to non-diabetic subjects (1.90%) .[11]

A meta-analysis and systematic review including over 12,000 people found a prevalence rate of 33% with a 95% CI of 24% to 41%, which was in agreement with our results. A statistically significant correlation between pancreatic steatosis prevalence and hypertension (T2D) and metabolic syndrome was found in the meta-regression study. Notably, nine of the eleven studies that formed the basis of this review took place in Asian populations. Because of this, we wonder if the results are generalizable to other populations .[23]

Recent studies have shown that pancreatic fatty infiltration was associated with increased incidence of (T2D)and poor glycemic control among obese individuals .[24]

Nadarajah et al., a notable disparity between the (T2D) and control groups for the pancreatic fat percentage. In regression analysis, the fat percentage within the pancreatic tail was the only variable that showed a significant difference between the control group and the group at risk for (T2D) (p=0.007). A pancreatic tail fat level over 10% demonstrated a sensitivity of 45.5% and specificity of 81.3% in predicting the onset of (T2D)during four years. [25]

In the current study, we found that BMI, ALT, AST, amylase, lipase, ALT, AST, cholesterol, LDL, TG, and HbA1c were positively correlated with the degree of the fatty pancreas with p values <0.01. At the same time, HDL was negatively correlated with the degree of fatty pancreas with a p-value of 0.013.

These findings are consistent with most evidence regarding the association between obesity, lipid profile, and (NAFLD) with the incidence of pancreatic lipomatosis .[26, 27]

Elevated liver transaminases are signs of hepatocellular damage and are linked to fatty liver disease. With a sensitivity of 67% and a specificity of 51%, patients with NAFLD and mild to moderate fibrosis (F1-F2) could be detected using a cutoff value of 59 U/L. A threshold value of 81 U/L was shown to be 53% sensitive and 67% specific for patients with severe fibrosis and cirrhosis (F3-F4) (28).

Many studies have shown that obesity and NAFLD are associated with a higher prevalence of pancreatic steatosis. Uygun et al. found that NAPL was significantly higher among NAFLD compared to the control group .[12] Additionally, Pacifico et al. found that hepatic fat fraction was associated with pancreatic fat fraction, and both are independent risk factors in the development of diabetes among obese and overweight children and adolescents .[11] similar findings were reported in earlier studies .[13, 14]

We found that BMI, TG, and LDL levels are independent predictors for fatty pancreas after adjusting for other risk factors such as cholesterol level, HDL, and HBA1c with p values <0.01.

Rossi et al. demonstrated that visceral adipose tissue .[16] assessed via MRI, is the primary determinant of ectopic fat accumulation in the liver and pancreas .[29] Al-Haddad et al. and Sepe et al. discovered that individuals with EUS fatty liver and higher BMI were separate factors that might predict the presence of a fatty pancreas .[30, 31]

Lee et al. reported that visceral fat, glycemic control, and ALT level were independent predictors for fatty pancreas in a multivariate logistic regression analysis, even after adjusting for age, body mass index, and lipid profile ($P < 0.05$). [32]

To our knowledge, this is the first study to assess the cutoff values of BMI, ALT, AST, and HbA1c that can significantly predict fatty pancreas, using cutoff points 30 kg/m2, 33 IU, 32 IU, and 7 %, with sensitivity 95%, 68.3%, 70.7%, 80.5%, and specificity 100%, 99.0%, 92.0%, and 97.5% respectively. The lipid profile can significantly predict fatty pancreas using cutoff point 220 mg/dl of cholesterol, 175 mg/dL of TG <33.5 mg/dl of HDL, and 160 mg/dl of LDL, with sensitivity 100%, and specificity 99-96% respectively.

The primary constraints of the present investigation lie in the inability to definitively establish the causal link between fatty pancreas, fatty liver (T2D), and obesity. Furthermore, we propose that additional cohort studies should be undertaken to ascertain the primary mechanism and sequence of events leading to the development of type 2 diabetes mellitus, fatty pancreas, and fatty liver. It is imperative to minimize confounding factors to identify the initial risk factor and its subsequent effects accurately.

4. Conclusion

Non-alcoholic pancreatic lipomatosis (NAPL) is significantly associated with type 2 DM, obesity, lipid profile, and glycemic control. The degree of fatty pancreas is significantly correlated with BMI, glycemic control, and lipid profile. BMI, ALT, AST, HbA1c, and lipid profile can significantly predict fatty pancreas among the general population.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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