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Non-Alcoholic Fatty Liver and Fatty Pancreas Diseases Associate with Acute Pancreatitis

Süleyman Ahbab[1,a], Ayşe Keskin[2,b], Emre Hoca[1,c*], Hayriye Esra Ataoğlu[1,d], Tuba Selçuk Can[3,e], Fatih Türker[1,f], Betül Çavuşoğlu Türker[4,g]

[1] University of Health Sciences Turkey, Haseki Health Training and Research Hospital, Internal Medicine Clinic, İstanbul, Turkey, [2] Department of Internal Medicine Araklı Bayram Halil State Hospital, Internal Medicine, Trabzon, Turkey, [3] University of Health Sciences Turkey, Haseki Health Training and Research Hospital, Department of Radiology, İstanbul, Turkey, [4] İstanbul Taksim Training and Research Hospital, Internal Medicine Clinic, İstanbul, Turkey

**Corresponding author*

Research Article

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ABSTRACT

Objective: Fat accumulation in the liver and pancreas are clinical manifestations of metabolic syndrome associated with inflammation. It aimed to investigate the effects of the computed tomography (CT) estimated non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAFPD) on the development of acute pancreatitis in this study.

Patients and methods: This retrospective and cross-sectional study consisted of 194 participants admitted to the hospital with an abdominal pain complaint and underwent an abdominal CT scan during the investigation of the differential diagnosis. Medical database records of patients were investigated. Groups were consisted of according to the presence of acute pancreatitis as study and control. Attenuation measurements of the liver and pancreas were determined according to abdominal CT.

Results: A statistical significance was observed for the development of acute pancreatitis when patients with normoglycemia were compared to patients with prediabetes and diabetes. Percentages of NAFLD and NAFPD according to the median of CT attenuation difference between pancreas and spleen values were elevated in the study group. A logistic regression model revealed that prediabetes, type 2 diabetes, NAFLD, and NAFPD, according to median value, were risk factors for acute pancreatitis (p<0.001, =0.001, =0.02, and =0.022).

Discussion: NAFLD and NAFPD, according to the median value of patients without pancreatitis, were determined as independent risk factors for the development of acute pancreatitis.

Keywords: Non-alcoholic fatty liver disease; non-alcoholic fatty pancreas disease; acute pancreatitis

Non-Alkolik Yağlı Karaciğer ve Yağlı Pankreas Hastalıkları Akut Pankreatit ile İlişkilidir

Süreç

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ÖZ

Amaç: Karaciğer ve pankreasta yağ birikimi metabolik sendromun klinik belirtileridir ve inflamasyonla ilişkilidir. Bu çalışmada bilgisayarlı tomografi (BT) ile tespit edilen non-alkolik yağlı karaciğer hastalığı (NAFLD) ve non-alkolik yağlı pankreas hastalığının (NAFPD) akut pankreatit gelişimi üzerindeki etkilerinin araştırılması amaçlandı.

Materyal ve Metod: Bu kesitsel retrospektif çalışma, karın ağrısı şikayeti ile hastaneye başvuran ve ayırıcı tanı sırasında tüm batın tomografisi çekilen 194 hastadan oluşturuldu. Hastaların tıbbi verileri hastane veri tabanı kayıtları kullanılarak incelendi. Gruplar akut pankreatit varlığına göre çalışma ve kontrol grupları olarak oluşturuldu. Abdominal BT ile karaciğer ve pankreasın atenüasyon ölçümleri yapıldı.

Bulgular: Normoglisemik hastalar hem prediyabetik hem de diyabetik hastalarla karşılaştırıldığında, akut pankreatit gelişimi için istatistiksel bir anlamlılık gözlendi. Pankreas ve dalak arasındaki BT atenüasyon farkının medyanına göre NAFLD ve NAFPD saptanma yüzdeleri çalışma grubunda yüksekti. Lojistik regresyon modelinde median değere göre prediyabet, tip 2 diyabet, NAYKH ve NAFPD'nin akut pankreatit için risk faktörleri olduğu gözlendi (sırasıyla, p<0,001, =0,001, =0,02 ve =0,022).

Sonuç: Pankreatiti olmayan hastaların median değerine göre NAYKH ve NAFPD, akut pankreatit gelişimi için bağımsız risk faktörleri olarak belirlendi.

Anahtar sözcükler: Non-alkolik yağlı karaciğer hastalığı, non-alkolik yağlı pankreas hastalığı, akut pankreatit

[a] *drsahbab@gmail.com* *https://orcid.org/0000-0001-9239-9132*
[b] *aysekeskin__@hotmail.com* *https://orcid.org/0000-0002-9455-1027*
[c] *emrehoca89@gmail.com* *https://orcid.org/0000-0003-4232-7362*
[d] *eataoglu@gmail.com* *https://orcid.org/0000-0002-6559-2575*
[e] *drtubas@gmail.com* *https://orcid.org/0000-0002-2388-1715*
[f] *fatihturker1985@hotmail.com* *https://orcid.org/0000-0002-8281-0319*
[g] *cavusoglubetul@hotmail.com* *https://orcid.org/0000-0002-8041-1904*

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Introduction

The prevalence of metabolic syndrome (MetS) and associated diseases are major health problems and increasing worldwide [1]. MetS is associated with abdominal obesity and visceral adipose tissue accumulation, mainly in the liver and pancreas [2]. Non-alcoholic fatty liver disease (NAFLD) is hepatic, and non-alcoholic fatty pancreas disease (NAFPD) is the pancreatic manifestation of MetS [3]. NAFLD may progress to steatohepatitis (NASH), fibrosis, and hepatic cirrhosis in lifespan [4]. NAFPD is preferred to be used when it is associated with obesity and metabolic syndrome. NAFPD seems to be a possible cause of inflammation, pancreatitis, and fibrosis, which yield pancreatic endocrine and exocrine insufficiency [5]. NAFLD is strongly linked with NAFPD, but this relationship is unclear [6]. Acute pancreatitis is a common disease with variable severity from being self-limited to fatal and usually develops due to gallstone, chronic alcohol intake, and familial hypertriglyceridemia [7].

Moreover, MetS and type 2 diabetes increase the risk of acute pancreatitis [8, 9]. There is limited knowledge about the relationship between the fatty liver, fatty pancreas, and pancreatitis in the literature [10, 11]. We aimed to evaluate the effect of NAFLD and NAFPD on the development of acute pancreatitis in this study.

Methods

Study participants

This is a retrospective study performed between 1st January 2016 and 1st January 2017 in the internal medicine clinic of Istanbul Haseki Training and Research Hospital, University of Health Sciences in İstanbul. The study protocol was approved by the local ethics committee of Istanbul Haseki Training and Research Hospital (Reference No. 30279032-000-20916). The ethics committee anonymized and approved the database information without consent. This study was conducted in accordance with the principles of good clinical practice and the declaration of Helsinki. Data for the study was derived from the electronic management system of the hospital. The medical records of 991 patients who applied to our hospital's internal medicine and emergency clinics for abdominal pain and underwent abdominal tomography (CT) for the differential diagnosis were investigated retrospectively (Figure 1).

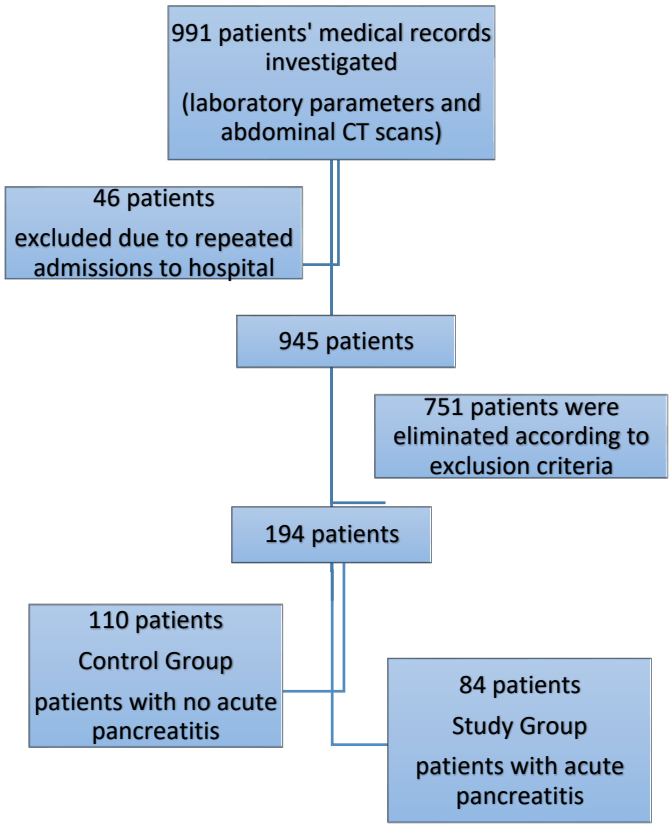

Figure 1. A tree diagram of patients was included and discarded in the study.

Patients without acute pancreatitis and emergency pathology requiring hospitalization were settled in the control group. Patients with acute pancreatitis after the investigation of the medical

records were consistent with exclusion criteria specified in the study group. Clinical pathologies that could affect CT measurements of the liver and pancreas were eliminated. Patients with gastrointestinal tract perforation, acute or chronic viral hepatitis, chronic pancreatitis, hepatic cirrhosis, peritonitis, chronic renal disease, sepsis, chronic heart failure, alcohol consumption, and malignancy were excluded from the study. Patients without alcohol consumption (current and at least within the last year) were included in this study. As a general definition, in non-alcoholic fatty liver and pancreas, daily intake of alcohol should be less than 30 gr/day for men and less than 20 gr/day for women. Also, patients with severe pancreatitis who required intensive care unit (due to clinical prognosis) follow-up and planned to undergo emergency surgery were not eligible and were not included in this study. In addition, patients with acute pancreatitis who developed poor clinical status, unstable vital signs, severe electrolyte imbalance, acute renal failure, and respiratory distress were followed up in the intensive care unit. In the severe clinical course of pancreatitis, pancreatic necrosis can affect pancreatic tissue integrity and CT-based tissue attenuations so that NAFPD cannot be determined correctly. Acute pancreatitis was described as who admitted to the hospital with; [1] acute abdominal pain and [2] an elevation in serum amylase and lipase levels, and [3] diagnostic CT scan findings. This study consisted of a total of 194 participants, 110 as control and 84 as study groups.

Biochemical parameters such as serum fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), creatinine, amylase, lipase, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cholesterol levels were analyzed by using Abbott Architect Analyzer System (IL, USA). Groups were classified according to the participant's medical history of diabetes and prediabetes. Prediabetes and type 2 diabetes mellitus were described according to the American Diabetes Association, Standards of Medical Care in Diabetes 2018 criteria. Prediabetes was defined as patients with FBG between 5.6-6.9 mmol/L and/or HbA1c 39-47 mmol/mol. Diabetes was defined as patients with FBG ≥ 7 mmol/L, 2 hours post-prandial glucose ≥ 11.1 mmol/L and/or HbA1c ≥ 48 mmol/mol.

Radiological Evaluation

Abdominal CT scans were performed using a 64-detector Philips CT device (Brilliance, Philips Medical Systems, Cleveland, Ohio, USA). Abdominal CT shots were performed according to the routine intravenous contrast-enhanced protocol (upper abdominal CT without axial contrast and whole abdominal CT taken in the portal venous phase at 60 seconds). Abdominal ultrasonography was performed for all study patients with acute pancreatitis as a first assessment then abdominal CT was carried out. Abdominal CT was performed after 6-72 hours from the admittance of the patients to the hospital. Abdominal CT images were reviewed prospectively and taken from pre-contrast axial sections using the INFINITT PACS version 3.0.11.4 (INFINITT Healthcare Co. Ltd. Korea) by two expert radiologists with five years of experience. Radiologists were blinded to patient's clinical data. Attenuation values of the liver, spleen, and pancreas were measured and expressed as Hounsfield Unit (HU). The liver attenuation was determined as the average of the measurements made from the right, left, and caudate lobes, respectively, and the attenuation spleen was determined by taking the average of three measurements made from the upper, middle, and lower parts of the spleen. Attenuation measurements of the pancreas on caput, corpus, and cauda were recorded separately. The arithmetic mean of these three measurements was determined as the mean attenuation HU value of the pancreas. Cyst, mass, calcification, and vascular structures were not included in the organ's attenuation measurements. CT estimated NAFLD was described as the liver and spleen attenuation difference (L-S value) < -10 HU [12, 13]. CT estimated NAFPD was defined as pancreas-spleen attenuation difference (P-S value) in negative HU value [14, 15]. The negative P-S value reflects the abdominal CT-based pancreatic steatosis. In this study, patients' P-S attenuation values were extremely wide ranges. For that reason, the median value of control patients was calculated as -7.00 HU (min: -50.70 and max: 11.00). The median value of the P-S attenuation difference of the control group was used to demonstrate the presence of NAFPD in the groups properly.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows. Numeric values were expressed as the mean ± standard deviation. Kolmogorov-Smirnov Z test was used to determine the distributions of variables. Regular variances were assessed using a t-test, and irregular variables were assessed using the Mann-Whitney U test. Chi-square test was used to evaluate categorical variables. A logistic regression analysis was performed to determine risk factors for acute pancreatitis. A p-value ≤ 0.05 and a 95% confidential interval were considered statistically significant.

Results

The Control group consisted of 110 (39 with normoglycemia, 43 with prediabetes, 28 with type 2 diabetes), and the study group was 84 (12 with normoglycemia, 48 with prediabetes, 24 with type 2 diabetes) patients with a statistical significance (p= 0.003) as shown in table 1. A statistical significance was observed for the development of acute

pancreatitis when patients with normoglycemia were compared to patients with prediabetes and type 2 diabetes (p<0.001, 0.016) in the study group. Patient glucose determination was performed at admission to the hospital and before the abdominal CT scanning. In addition, patients were diagnosed with prediabetes and type 2 diabetes by taking into consideration blood tests performed in the hospital and recorded in the medical database within one year. Type 2 diabetes and prediabetes were based not only on the blood tests in the emergency laboratory. The scores of 84 patients with acute pancreatitis included in this study were calculated according to Ranson's criteria at the first admission to the hospital. No statistically significant correlation was found between abdominal CT-based NAFPD and calculated Ranson's scores in patients with acute pancreatitis (r: -0.169, p: 0.130). Etiologic examination of patients with acute pancreatitis revealed no specific cause in 65 patients except for risk factors such as diabetes and prediabetes. In the rest, cholelithiasis (14 patients) and hypertriglyceridemia (5 patients) were detected. In this study, the serum level of triglyceride above 1000 mg/dl was responsible for the cause of acute pancreatitis. The mean age was 61.16 ± 14.36 in the control group and 51.81 ± 17.73 in the study group. FBG and HbA1c levels were elevated in the study group compared to controls (p <0.001 and 0.035). AST, ALT, amylase, and lipase levels were significantly elevated in the study group (p<0.001). Total cholesterol, triglyceride levels, and ALT/AST ratio were not different between groups. CT estimated liver HU values of mean attenuation and difference between liver and spleen (L-S value) were decreased in the study group (p<0.001 and <0.001), as shown in Table 2. Moreover, the percentage of NAFLD and NAFPD according to the median value of the P-S attenuation difference of the control group was significantly high in the study group (p= 0.003 and 0.042). A logistic regression model revealed decreased age, prediabetes, and type 2 diabetes were risk factors for acute pancreatitis. It was found that NAFLD and NAFPD have 3.7 and 2.2 times fold additional risk for acute pancreatitis (Table 3).

Table 1. Comparison of characteristics and laboratory parameters between groups.

	Control Group *(n:110)*	**Study Group** *(n:84)*	**P value**
Gender (male/female)	59/51	54/30	0.136
NormoGly / PreDM / DM (n)	39 / 43 / 28	12 / 48 / 24	***0.003***
Age	61.16 ± 14.36	51.81 ± 17.73	***<0.001***
FBG (3.9-6.1 mmol/L)	6.09±2.18	8.49±4.19	***<0.001***
HbA1c (20-48 mmol/mol)	43.1±8.5	49.4±10.1	***0.035***
Creatinine (53-106 µmol/L)	83.10±68.07	90.17±59.23	0.468
ALT (0.17-0.68 µkat/L)	0.47±0.75	1.37±2.11	***<0.001***
AST (0.17-0.58 µkat/L)	0.45±0.53	1.59±2.56	***<0.001***
Amylase (0.46-1.67 µkat/L)	1.34±0.69	12.02±12.60	***<0.001***
Lipase (0.08-1.12 µkat/L)	0.55±0.68	28.17±30.22	***<0.001***
Total cholesterol (<5.18 mmol/L)	5.14±1.20	4.74±2.56	0.20
Triglyceride (<1.69 mmol/L)	1.71±0.85	2.77±4.90	0.063
ALT/AST ratio	1.21±0.57	1.39 ± 0.78	0.081

(NormoGly: normoglycemic patients, PreDM: patients with prediabetes, DM: patients with type 2 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, ALT: alanine aminotranspherase, AST: aspartate aminotransferase, HDL: high density lipoprotein, LDL: low density lipoprotein)

(Statistical significant p values were expressed in bold and italic)

Table 2. Comparison of CT estimated attenuation (HU) values of the liver and pancreas between groups

	Control Group *(n:110)*	**Study Group** *(n:84)*	**P value**
Liver (HU)	53.19±9.10	46.74 ± 11.85	***<0.001***
Pancreas (HU)	36.96± 11.71	36.20± 8.93	0.620
Spleen (HU)	47.21±5.50	46.56±4.99	0.766
L-S value (HU)	5.98±9.27	0.18±11.94	***<0.001***
P-S value (HU)	-10.25± 12.04	-10.36±9.14	0.943
NAFLD (n - %)	6 - 5.5%	16 - 19%	***0.003***
NAFPD (n - %)	56 - 50.9%	55 - 65.5%	***0.042***

(HU: Hounsfield unit, L-S value: difference between liver and spleen, P-S value: difference between pancreas and spleen, NAFLD: non-alcoholic fatty liver disease, NAFPD: non-alcoholic fatty pancreatic disease, n: number of patients,)

(Statistical significant p values were expressed in bold and italic)

Table 3. A logisitic regression analysis model for the risk of acute pancreatitis in the study group

	OR	95% CI	P value
Age	0.951	0.930 - 0.973	***<0.001***
Glycemic Category			***0.001***
Prediabetes	5.335	2.188 - 13.009	***<0.001***
Type 2 diabetes	5.523	2.059 -14.817	***0.001***
NAFLD	3.741	1.233 - 11.347	***0.02***
NAFPD	2.244	1.126 - 4.472	***0.022***

(OR: odds ratio, CI:confidence interval, NAFLD: non-alcohoic fatty liver disease, NAFPD: non-alcoholic fatty pancreatic disease)

(Statistical significant p values were expressed in bold and italic)

Discussion

In this study, prediabetes and diabetes were significantly higher in patients with acute pancreatitis than in controls. Type 2 diabetes and prediabetes were closely associated with acute pancreatitis. It was found that diabetes and prediabetes had a 5.5-fold increase and a 5.3-fold increase in the risk of acute pancreatitis, respectively. Diabetes, obesity, and MetS are risk factors for acute pancreatitis (16). Essentially, metabolic parameters are associated with a pro-inflammatory process and accelerate the development of acute pancreatitis [16]. Impaired fasting glucose, prediabetes, and type 2 diabetes are the major criteria of MetS. The main pathology is insulin resistance. MetS and obesity are closely associated with the development and course of acute pancreatitis [17, 18]. In this study, age was closely related to acute pancreatitis. Age was significantly lower in patients who underwent pancreatitis than in the control. Type 2 diabetes is a well-known risk factor for developing pancreatic steatosis and pancreatitis. Of the 110 patients in the control group, 39 (35.5%) were with normoglycemia, and 71 (64.5%) with prediabetes and diabetes. 12 (14.3%) of 84 patients with acute pancreatitis were normoglycemia, and 72 (85.7%) of them were with prediabetes and type 2 diabetes in this study. Moreover, pancreatitis develops more frequently in the 4th and 5th decades [19]. In our study, acute pancreatitis was significantly higher in NAFPD and NAFLD patients. NAFLD was observed in 19% of the patients with acute pancreatitis, and it was 5.5% in the control group (p: 0.003). The percentage of NAFPD, according to the median value, was 65.5% of the patients with acute pancreatitis. There was a significant increase in NAFLD and NAFPD among patients with acute pancreatitis. In addition, according to the median value, NAFPD was detected in approximately 50% of the control patients. These results suggest that an increase in the accumulation of pancreatic fat content may start from younger ages and progress with the presence of risk factors. Fat accumulation in the pancreas plays a key role in developing pancreatitis [20]. Weng et al. reported that fatty pancreas and liver increase independently with age, obesity, and diabetes [21]. Rossi et al. reported that visceral obesity is the main determinant of a fatty pancreas and liver [22]. In this study, the percentage of NAFPD according to median value in patients with pancreatitis (65%) was higher than that of NAFLD (19%). This may be related to pancreatic fat accumulation being more widespread than in the liver. Moreover, fat accumulation in the pancreas may have started earlier before the steatosis in the liver. The increase in adipose tissue in the pancreas and liver are associated with low-grade local inflammation. Inflammatory cytokines (TNF-alpha, IL-6, monocyte chemotactic factor-1) from adipose tissue and local macrophages and TGF-beta release stimulate fibroblasts [23 - 25]. This process increases the tendency to acute pancreatitis because of the fatty progression of the pancreas. In our study, the risk of acute pancreatitis was 2.2 times higher in patients with NAFPD and 3.7 times higher in patients with NAFLD, according to regression analysis. NAFPD and NAFLD are found as independent risk factors for pancreatitis. Some publications have demonstrated that NAFPD leads to the endocrine and exocrine dysfunction of the pancreas. NAFPD has a prognostic significance in patients with acute pancreatitis [26, 27]. In obese patients, pancreatic steatosis has been shown to increase inflammation during acute pancreatitis, resulting in more severe parenchymal damage [28, 29]. Ranson score is used to predict the prognosis. An increase in the Ranson score indicates the severity of acute pancreatitis. In the severe clinical course of pancreatitis, pancreatic necrosis affects pancreatic tissue integrity and CT-based tissue attenuations. Therefore, determination of NAFPD becomes difficult, and these patients who settled in the intensive care unit were not included in the study. There was no

significant relationship between the two groups regarding Ranson scores.

There are some limitations to this cross-sectional, retrospective study. First, the study was based on only CT scan measurements of the pancreas and liver. Abdominal CT results were examined electronically on the computer. Other radiological methods besides CT may be applied for estimating the fat contents of the liver and pancreas as external validation. Anthropometric measurements could not be provided for all patients because some patients lacked medical records. To calculate insulin resistance, serum insulin levels were not routinely analyzed for all patients. Insulin resistance and anthropometric measurements are important findings to identify the presence of MetS.

Abdominal ultrasonography was performed for all study patients with acute pancreatitis as a first assessment then abdominal CT was carried out as required. In 65 patients with pancreatitis, biliary cause, like cholelithiasis, was not detected because of radiological examinations. In this retrospective-designed study, patients with pancreatitis do not reflect the real rate in the population because chronic pancreatitis patients with recurrent hospitalization and alcohol-related pancreatitis were omitted. Microlithiasis and viral agents other than the hepatitis A, B, and C viruses that cause acute pancreatitis cannot be eliminated. Other viral markers are not routinely examined in the hospital's laboratory. This study will provide ideas for further studies with a more significant number of patients.

Conclusion

In conclusion, NAFLD and NAFPD according to the median value of patients without pancreatitis, were determined as independent risk factors for developing pancreatitis. Diabetes and prediabetes were also independent risk factors for acute pancreatitis.

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Conflicts of Interest: The authors declare no conflict of interest.

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