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Determinants of Pancreatic Steatosis: A Retrospective Observational Study

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ABSTRACT

BACKGROUND

Metabolic syndrome affects 35% of the adult population in developed countries associated with non-alcoholic steatohepatitis, insulin resistance, and cardiovascular events. Fatty infiltration of the pancreas, or pancreatic steatosis, is a risk factor for acute pancreatitis, pancreatic malignancies, and diabetes mellitus, yet its relationship with metabolic syndrome is not well defined.

METHODS

We performed a single-centered retrospective observational study of 322 healthy subjects (subjects volunteering to be kidney transplant donors, mean age=46.3±13.5, 163 men and 159 women) in the last 2 years (July 2018-February 2020) from our institution. Pancreatic steatosis and hepatosteatosis were confirmed by computed tomography.

RESULTS

Pancreatic steatosis was present in 26.3% (85/322) of the subjects, and this finding correlated with age, body mass index (BMI), male sex, a family history of diabetes, creatinine, cystatin C, uric acid, low-density lipoprotein (LDL) cholesterol, triglycerides, glycemia, hemoglobin, transverse body diameter, and subcutaneous fat thickness levels by univariable logistic regression. On multiple linear regression only age (95% CI 1.01, 1.06), BMI (95% CI 1.01, 1.19), male sex (95% CI 1.49-5.99), uric acid (95% CI 1.01, 1.76), and subcutaneous fat thickness levels (95% CI 1.21-2.36) remained independently associated with pancreatic steatosis.

CONCLUSION

Pancreatic steatosis is common and associated with obesity, elevated serum uric acid, subcutaneous fat thickness, and male sex. Future studies are needed to evaluate if there are specific clinical consequences to the presence of pancreatic steatosis.

KEYWORDS:
Visceral steatosis, Uric acid, Liver steatosis, Obesity

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INTRODUCTION

Metabolic syndrome is considered a medical pandemic that affects approximately 35% of the adult population in western countries leading to significant comorbidities including diabetes mellitus, pro-thrombotic and proinflammatory state, cardiovascular events, and non-alcoholic fatty liver disease (NAFLD).[1,2] As the global incidence of metabolic syndrome is on the rise, the associated comorbidities gain importance, among which pancreatic steatosis is a newly recognized concept.[3] Cadaveric studies performed by Ogilvie in 1933 indicated higher pancreatic fat (17%) in obese cadavers compared with lean cadavers (9%), while a limited number of radiological studies demonstrated a similar correlation.[4-7] Additionally, a few studies noted a frequent coexistence of NAFLD and pancreatic steatosis,[8-10] while others reported the correlation of pancreatic steatosis with the severity of acute pancreatitis.[11,12] Fatty infiltration of the liver and other tissues has been linked to an increase in the production of certain adipokines such as leptin and adiponectin and of different proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, interleukin-1β myeloperoxidase, and monocyte chemotactic protein-1.[13-15] Although animal studies demonstrated a link between fatty pancreatic infiltration and beta-cell dysfunction, human studies revealed contradictory findings regarding the emergence of insulin resistance or diabetes mellitus.[16-19] There is a need for more studies for identifying risk factors and comorbidities associated with pancreatic steatosis since early detection and intervention, such as caloric restriction and weight loss, have been shown to reverse the condition.[20]

Here we performed a single-center retrospective study to determine the association between pancreatic steatosis assessed via imaging studies and laboratory and clinical features in a cohort of healthy participants.

MATERIALS AND METHODS

Study Design:

We performed a single-center retrospective observational study including all 327 healthy renal transplantation donors in the last 2 years (July 2018-February 2020) from our institution. The study was approved by the Ethics Committee of the Koc University School of Medicine. Baseline laboratory values of the patients included kidney function tests (serum creatinine, estimated glomerular filtration rate (eGFR), cystatin C), liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct and total bilirubin, alkaline phosphatase (ALP)), uric acid, complete blood count, 24-hour proteinuria, spot urine albumin-creatinine ratio, fasting glucose, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and thyroid-stimulating hormone were recorded. Additionally, family history (i.e. cardiovascular disease, chronic disease, chronic liver disease, and diabetes mellitus), physical measurements (i.e. body mass index [BMI], systolic and diastolic blood pressure) and social features of the participants (i.e. smoking and alcohol consumption) were recorded. Computed tomography (CT) scans were employed to assess transverse body diameter, subcutaneous fat thickness, and hepatic and pancreatic steatosis. Details of the radiological process can be accessed in the following section. We excluded five participants with inadequate laboratory and imaging data.

Imaging Analysis:

All images were performed on a Siemens CT scanner, either 64-slice (Somatom) or 256-slice (Definition Flash). Unenhanced axial CT images at 2-mm slice thickness and kVp values ranging between 80-140 kVp were used. All images were reviewed by one of two radiologists (E.A. and S.G.) with over 10 years of experience in reading abdominal CT.

Measurements were performed on an independent General Electric workstation. Three regions of interest (ROIs) were drawn on the right and left lobes of the liver and spleen (upper/middle/lower pole). To ensure reproducibility of the measurements, the ROIs were drawn to avoid vessels, focal lesions, and parenchymal calcifications. The density values were noted in Hounsfield Unit (HU). Data were tabulated into Microsoft Excel and means calculated thereof.

Hepatic steatosis was defined as a mean hepatic density at least 5 HU less than the mean splenic density ("severe" if the difference exceeded 10 HU, otherwise "mild-to-moderate").[21]

Similarly, five different ROIs were drawn in the unci-

nate process, head, neck, body, and tail of the pancreas. Densities were tabulated and means calculated as above. Pancreatic steatosis was defined as "present" if the mean pancreatic density was at least 5 HU less than that of the spleen.[22] The widest axial abdominal diameter was measured. Axial subcutaneous fat thickness was always measured in the anterior-to-posterior direction at the periumbilical region. Psoas muscle cross-section area was measured using free-hand ROI at the level of L3.

Statistical analysis:

Variables were expressed as median with interquartile range, mean ± standard deviation or as percent frequency, as appropriate. Between-groups comparisons were assessed for nominal variables with the Chi-square or Fisher's tests and by independent-samples t test or Mann–Whitney test for the rest of the variables. The distribution of the variables was assessed using the Shapiro-Wilk test.

Logistic regression analysis was used to assess the variables associated with pancreatic steatosis. Those variables with $p<0.05$ by univariate analysis were included in the backward stepwise multivariate logistic regression analysis model, and the respective odds ratios (ORs) with 95% confidence intervals (CIs) were determined.

All analyses were performed using Stata MP software, version 13 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). A two-tailed $p<0.05$ was considered to be significant.

RESULTS

Patient Demographics

322 patients were included. The mean age was 46.3±13.5 years. 163 patients (50.6%) were men, and 126 (39.1%) were active smokers. Other clinical and biological characteristics of the subjects are presented in table 1.

We divided the patients into two groups based on the presence of pancreatic steatosis (table 1). Patients with this pathology were older, had higher BMI values, and were more likely to be men, have a family history of diabetes and hepatic steatosis. Furthermore, these patients also had higher creatinine, cystatin C, uric acid, LDL cholesterol, triglycerides, hyperglycemia, ALT, hemoglobin, transverse body diameter, and subcutaneous fat thickness levels but lower eGFR values than patients without pancreatic steatosis (table 1). Univariate logistic regression analysis demonstrated a positive correlation with age, BMI, male sex, a family history of diabetes, creatinine, cystatin C, uric acid, LDL cholesterol, triglycerides, glycemia, ALT, hemoglobin, transverse body diameter, and subcutaneous fat thickness levels, and negatively associated with eGFR (table 2).

In a multiple linear regression model, including all these predictors of pancreatic steatosis, only age, BMI, male sex, uric acid, and subcutaneous fat thickness levels remained independently associated with pancreatic steatosis.

DISCUSSION

We demonstrated an independent association between age, BMI, male sex, uric acid, subcutaneous fat thickness, and pancreatic steatosis in our single-center retrospective observational study that included 322 healthy participants. The primary finding was that pancreatic steatosis appears to be a part of the constellation of findings associated with metabolic syndrome as well as age. Prior studies have correlated pancreatic steatosis with age.[17,23-25] and BMI,[16,24,26] while being inconclusive for serum lipid profile,[16,22,25,27] visceral adipose tissue,[24-27] beta-cell function.[16,22,24,26,28-30] liver function tests,[8-10,22] and uric acid.[31, 32] Here we identified elevated serum uric acid and subcutaneous fat thickness as independent risk factors for pancreatic steatosis. Although in the univariable analysis, we observed a relationship between pancreatic steatosis and renal function (as assessed by either serum creatinine, cystatin C, or eGFR), in the multivariable analysis, this association was lost. Thus, our study is important by showing that in healthy people, there is no association between kidney function and pancreatic fat infiltration. The role of uric acid as an independent risk factor for pancreatic steatosis, although the renal function is not, raises further questions regarding the indirect role of uric acid in the pathophysiology that may be related to a chronic inflammatory state, insulin resistance, hepatosteatosis, and vascular dysfunction associated with hyperuricemia.[33-35]

In the diagnosis of pancreatic steatosis, CT is the most commonly used imaging modality in the literature. In a study comparing unenhanced CT density of the pancreas and histopathology, Kim and colleagues found that the histologic pancreatic fat fraction was significantly correlated with the

Table 1: Baseline characteristics of the study population.

Variables	All (N=322)	No steatosis (N=237)	With Steatosis (N=85)	p
Age, years	46.3±13.5	44.4±13.0	51.5±13.5	<0.001
BMI, kg/m^2	26.6±4.3	25.8±3.9	28.7±4.4	<0.001
Male, n (%)	163 (50.6)	107 (45.2)	56 (65.9)	0.001
Smoking, n (%)	126 (39.1)	91 (38.4)	35 (41.2)	0.65
Alcohol consumption, n (%)	42 (13.0)	31 (13.1)	11 (12.9)	0.97
Family history of diabetes, n (%)	85 (26.4)	53 (22.4)	32 (37.7)	0.01
Family history of CVD, n (%)	51 (15.8)	40 (16.9)	11 (12.9)	0.39
SBP, mmHg	117.1±9.0	116.5±8.9	118.7±9.3	0.06
DBP, mmHg	74.6±7.8	74.5±7.8	74.8±7.8	0.79
Creatinine, mg/dL	0.79±0.16	0.78±0.16	0.84±0.15	0.01
Cystatin C, mg/L	0.87±0.16	0.85±0.15	0.94±0.18	<0.001
eGFR, ml/min/1.73 m^2	107.9±23.2	110.1±22.2	101.6±24.9	0.004
Uric acid, mg/dL	4.7 (4.0-5.8)	4.5 (3.8-5.4)	5.9 (4.4-6.5)	<0.001
Serum albumin, g/dL	4.65±0.29	4.64±0.29	4.68±0.26	0.21
Total cholesterol, mg/dL	187.0 (160.0-219.0)	185.0 (158.0-215.0)	197.0 (164.0-226.0)	0.06
HDL cholesterol, mg/dL	49.0 (41.0-59.0)	50.0 (41.0-60.0)	45.0 (39.0-56.0)	0.06
LDL cholesterol, mg/dL	130.0 (102.0-157.0)	124.0 (101.0-151.0)	138.0 (110.0-164.0)	0.01
Triglycerides, mg/dL	106.0 (77.0-149.0)	104.0 (76.0-143.0)	124.0 (96.0-154.0)	0.01
Glycemia, mg/dL	95.4±6.7	94.9±6.8	96.9±6.3	0.02
ALT, U/L	15.0 (11.0-20.0)	15.0 (11.0-19.0)	17.0 (14.0-25.0)	0.003
AST, U/L	16.0 (14.0-20.0)	16.0 (13.0-19.0)	16.0 (15.0-20.0)	0.06
ALP, IU/L	70.0 (57.0-86.0)	68.0 (56.0-85.0)	74.0 (62.0-87.0)	0.09
Total bilirubin, mg/dL	0.47 (0.30-0.64)	0.47 (0.30-0.64)	0.47 (0.30-0.63)	0.89
Direct bilirubin, mg/dL	0.20 (0.15-0.26)	0.20 (0.15-0.26)	0.20 (0.16-0.27)	0.68
WBC, *10^3/mm^3	7.4±1.9	7.3±1.9	7.7±1.9	0.13
Hemoglobin, g/dL	13.8±1.6	13.7±1.6	14.2±1.5	0.01
Platelets, *10^3/mm^3	254.5 (221.0-292.0)	253.0 (219.0-293.0)	256.0 (231.0-288.0)	0.71
TSH, mIU/L	1.7 (1.2-2.5)	1.7 (1.1-2.5)	1.8 (1.3-2.3)	0.50
UACR, mg/g	4.9 (2.9-12.7)	4.9 (2.9-10.0)	5.0 (2.9-26.2)	0.12
24-hour proteinuria, mg/day	108.1 (88.0-134.6)	109.0 (88.0-132.2)	107.8 (87.3-144.9)	0.84
Transverse body diameter, cm	34.5±3.9	33.7±4.0	36.6±2.9	<0.001
Subcutaneous fat thickness, cm	2.7±1.1	2.5±1.1	3.2±1.0	<0.001
Hepatic steatosis, n (%)				
Severe steatosis	9 (2.8)	5 (2.1)	4 (4.7)	<0.001
Moderate steatosis	43 (13.4)	21 (8.9)	22 (25.9)	
No steatosis	270 (83.9)	211 (89.0)	59 (69.4)	

Data are expressed as mean ± SD, median with IQR, or percent frequency, as appropriate.
UACR – urinary albumin to creatinine ratio; ALP – alkaline phosphatase; ALT – alanine transaminase; AST – aspartate transaminase; BMI – body mass index; CVD – cardiovascular disease; DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate; HDL – high-density lipoprotein; LDL – low-density lipoprotein; SBP – systolic blood pressure; TSH – thyroid-stimulating hormone ; WBC – white blood cells.

Table 2: **Univariable and multivariate logistic regression**

Univariable analysis	OR	95% CI
Age, per 1 year increase	1.04	1.02-1.06
BMI, per 1 kg/m^2 increase	1.19	1.11-1.27
Sex (Ref. Female)	2.35	1.40-3.93
Family history of diabetes (Ref. No history)	2.09	1.23-3.58
Glycemia, per 1 mg/dL increase	1.05	1.01-1.09
Creatinine, per 1 mg/dL increase	8.91	1.87-42.49
Cystatin C, per 1 mg/L increase	31.50	6.47-153.34
eGFR, per 1 ml/min/1.73 m^2 increase	0.98	0.97-0.99
Hemoglobin, per 1 g/dL increase	1.24	1.06-1.46
Uric acid, per 1 mg/dL increase	1.88	1.51-2.35
LDL cholesterol, per 10 mg/dL increase	1.07	1.01-1.14
ALT, per 10 U/L increase	1.31	1.05-1.65
Transverse body diameter, per 1 cm increase	1.24	1.15-1.34
Subcutaneous fat thickness, per 1 cm increase	1.88	1.46-2.43
Hepatic steatosis (Ref. No hepatic steatosis)	3.58	1.93-6.62

Multivariable analysis	OR	95% CI
Age, per 1 year increase	1.04	1.01-1.06
BMI, per 1 kg/m^2 increase	1.10	1.01-1.19
Sex (Ref. Female)	2.99	1.49-5.99
Uric acid, per 1 mg/dL increase	1.33	1.01-1.76
Subcutaneous fat thickness, per 1 cm increase	1.69	1.21-2.36

(ALT – alanine transaminase; BMI – body mass index; eGFR – estimated glomerular filtration rate; LDL – low-density lipoprotein)

difference between pancreatic and splenic attenuation.[36] In this study, sensitivity and specificity of pancreatic steatosis were found 79.3% and 42.4%, respectively. Another study investigating the correlation between pancreatic steatosis and metabolic syndrome also used unenhanced CT as the reference standard.[21] In this study, -5 HU was used as a cut-off for and pancreatic steatosis values less than -5 HU was considered as the fatty pancreas. In our study, we applied the same cutoff to our cohort. In order to increase the accuracy of density measurements, as much as pancreatic and splenic tissue were included. Therefore, multiple ROIs were drawn in all anatomical segments of the pancreas as well as the spleen, which was described in the methods section.

Our study provides new data on the prevalence and risk factors of pancreatic steatosis in participants with no pre-existing medical condition. The limitations of our analysis include being a single-center retrospective study and also being unable to identify long-term outcomes of such associations. As pancreatic steatosis has been shown as a risk factor for certain medical conditions, like acute pancreatitis, diabetes mellitus, or non-alcoholic steatohepatitis and also that earlier intervention is likely to reverse the condition, identification of high-risk patients could have great significance in preventive medicine.

In conclusion, pancreatic steatosis is a common finding and associated with obesity, serum uric acid, subcutaneous fat thickness, and sex. Future large-scale prospective studies are needed for more comprehensive identification of the importance of pancreatic steatosis on the development of systemic disease.

Significance of this study:

- Pancreatic steatosis is a common finding.

- Pancreatic steatosis is associated with obesity, serum uric acid, subcutaneous fat thickness and gender.
- Future large scale prospective studies are needed for more comprehensive identification of the importance of pancreatic steatosis on development of systemic disease

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Compliance with Ethical Standards:

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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