Original Research Article

Pancreatic Fat Accumulation: A Link to Pre-diabetes and Diabetes Mellitus

ABSTRACT

Objective: The study focused on elucidating the presence of pancreatic steatosis in pre-diabetes and diabetes mellitus along with investigating the correlation between pancreatic steatosis and metabolic parameters.

Methods: This research involved 314 patients who sought treatment at internal medicine outpatient and inpatient clinics from April 2022 to May 2023. Patients who underwent non-enhanced abdominal computed tomography for any reason were included in the study. The patients were categorized into three groups: healthy controls(n=103), diabetes individuals(n=109), and prediabetes individuals(n=102).

Results: The study aimed to explore the relationship between pancreatic steatosis and metabolic parameters. The findings revealed that HDL level, albumin, and glomerular filtration rate (GFR) showed a positive correlation with pancreatic density, indicating a lower degree of steatosis in the pancreatic tissue. Conversely, patients with higher levels of HbA1c, uric acid, blood glucose levels, body mass index, INR exhibited a higher degree of pancreatic steatosis.

Furthermore, the research identified the presence of pancreatic steatosis in prediabetes patients. There was no significant difference in pancreatic steatosis between prediabetes and diabetes patients, suggesting that their pancreatic densities were statistically similar(p=0,08).

Conclusion: Our study investigated pancreatic steatosis in diabetes and pre-diabetes patients, and its relationship with metabolic parameters.The findings suggest that pancreatic steatosis is also present in the prediabetes phase and it has a correlation with metabolic parameters seen in diabetes process.

Keywords: Diabetes mellitus, prediabetic state, steatosis, hemoglobin A1c protein

Introduction

Type 2 diabetes mellitus is characterized by a gradual decline in pancreatic beta cells, resulting in hyperglycemia. Currently, diabetes mellitus is regarded as equivalent to

cardiovascular disease. However, the precise cause of beta cell loss in type 2 diabetes mellitus remains elusive. The primary mechanism contributing to the observed insulin resistance in type 2 diabetes mellitus is believed to be a reduction in insulin secretion from pancreatic beta cells. This damage to beta cells is hypothesized to stem from metabolic stress and inflammation(1, 2).

Prediabetes is acknowledged as an intermediate phase between normal blood glucose levels and the elevated glucose levels observed in type 2 diabetes mellitus. In this stage, individuals may demonstrate impaired fasting blood glucose and/or impaired glucose tolerance.

Pancreatic steatosis refers to the accumulation of fat in pancreatic tissue, leading to the replacement of the normal pancreas parenchyma(3). This condition can be induced by various factors, including viral infections, pancreatitis, neoplasms, diabetes mellitus, aging, and hypercholesterolemia(4). Nevertheless, the association between pancreatic steatosis and the pathophysiological mechanisms of diabetes mellitus, as well as its influence on the progression of diabetes mellitus, remains unclear(5).There is a scarcity of studies examining the connection between prediabetes, diabetes, and pancreatic steatosis. Some researchers propose that insulin resistance is an outcome of a fatty pancreas, while others maintain opposing views(6).

The objective of the mentioned study is to investigate the correlation between a fatty pancreas and metabolic parameters. Through an exploration of the relationship between pancreatic steatosis and pancreatic tissue damage, we aim to gain insights into its role in the development of diabetes mellitus.

Materials and Methods

This is a cross-sectional retrospective research study. The data of patients admitted to internal medicine outpatient and inpatient clinics between April 2022 and May 2023 were collected from the databases. The study comprised three groups: the control group included patients with fasting blood glucose levels below 100 mg/dl, the prediabetes group included patients with fasting blood glucose levels between 100-126 mg/dl, and the diabetes group included patients with blood glucose levels >126 mg/dl.

For all groups, patients who had undergone abdominal non-enhanced computed tomography for any reason were included in the research. A total of 314 participants (195 male, 119

female), aged 18 years and older, were included in our project. Participants were selected randomly based on their admission date.

Patients meeting the following criteria were excluded from the study: age <18 or >80 years old, nephrotic-level proteinuria, intake of antioxidant and vitamin supplements, chronic kidney disease stage ≥3, pancreas neoplasm (primary or metastatic), history of pancreatitis, and history of pancreas surgery.

This study received approval from the local ethics committee and various demographic data and laboratory parameters of the patients were retrospectively collected and examined from available medical records and the hospital database system. Demographic data included age, sex, BMI (body mass index), alcohol consumption, and cigarette history. The collected and analysed laboratory parameters comprised GFR (glomerular filtration rate), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), INR (international normalized ratio), HbA1c (glycated hemoglobin), complete blood count, uric acid, bilirubin levels, total lipid profile, fasting blood glucose levels, and post-OGTT (oral glucose tolerance test) levels. Additionally, serum albumin levels were also considered.Obesity was defined as having a BMI equal to or greater than 30.

In the study, radiologic images were retrieved from a database, and these images were acquired using 128-sliced tomography (GE Healthcare, Chicago, USA). Contrast-enhanced tomography images were excluded from the study. The abdominal computed images were subsequently scrutinized by two different radiology specialists simultaneously. These specialists were blinded to the medical status of the subjects to maintain objectivity.The findings of their examination were recorded and demonstrated agreement.

The densities of the liver, pancreas, and spleen parenchyma were quantified in Hounsfield Units (HU) utilizing a 0.5 cm² elliptical region of interest (ROI). Liver density measurements involved separate assessments of the right lobe, left lobe, and caudate lobe. In the case of spleen density calculations, the upper, middle, and lower parts were examined, and the mean of these measurements was recorded. This meticulous approach to image analysis ensured precise and dependable assessment of the radiologic data in the study.

Statistical analysis

All statistical analyses were conducted using SPSS software, version 21.0 (SPSS, Inc., Chicago, IL, USA). Normally distributed continuous variables were presented as means ± standard deviation (SD). For continuous variables that did not follow a normal distribution, the comparison between groups was performed using the Kruskal-Wallis test. The Student's t-test was employed to assess differences between the pancreatic steatosis and non-pancreatic steatosis groups. Binary logistic regression was used to evaluate independent risk factors associated with pancreatic steatosis. The relationship between pancreatic steatosis and metabolic parameters was determined using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

The average ages of the control, prediabetes, and diabetes groups were 50.2 ± 17.4, 57.6 ± 13.3, and 61.3 ± 11.7 years, respectively. The diabetes group was significantly older than the other groups (p < 0.01). The mean weight was 72.2 kg in the control group, 77.9 kg in the prediabetes group, and 81.8 kg in the diabetes group. Both prediabetes and diabetes patients had a higher weight compared to the control group (p < 0.01). There were no significant differences in alcohol consumption and smoking status among the three groups. Detailed clinical data of the patients are presented in Table 1.

In terms of laboratory findings, the diabetes group exhibited elevated creatinine levels (1.65 ± 1.28 mg/dl) in comparison to the control (0.97 ± 0.42 mg/dl) and prediabetes (0.98 ± 0.36 mg/dl) groups (p < 0.05). Urea and uric acid levels were also higher in the diabetes group (p < 0.05). Fasting blood glucose and 2-hour postprandial glucose levels were significantly elevated in the diabetes group (p < 0.05). GFR levels were lower in the diabetes and prediabetes groups compared to the control group (p < 0.05). Detailed biochemical results of the patients are presented in Table 2.

Pancreatic fat accumulation was observed to be higher in the pancreatic head and lower in the pancreatic tail region. Pancreatic tissue density decreased, and pancreatic fat deposition increased in the diabetes group across all parts of the pancreas (p < 0.001). The measurements of pancreas densities in Hounsfield Units (HU) are presented in Table 3.

To investigate the effects of clinical variables on pancreatic fat accumulation, logistic regression analysis was conducted. The data were analysed in subgroups, such as pancreatic head fat accumulation and pancreatic body and tail fat group (N=314). It was determined that BMI > 30, HDL level < 60 mg/dl, uric acid level > 7 mg/dl, albumin < 3.4 g/dl, GFR < 89

ml/dl/1.73m², and HbA1c (refer to Figure 1) were statistically associated with pancreatic steatosis (p < 0.05).

Discussion

The nature and clinical implications of pancreatic steatosis, or pancreatic fat accumulation, continue to be a subject of debate. Some studies suggest that pancreatic steatosis may lead to inflammation of the pancreas and degeneration of acinar cells(7). Additionally, it has been suggested that fat in the pancreas may function as an endocrine organ, secreting adipocytokines that promote macrophage infiltration(8). While previous research has linked pancreatic steatosis with diabetes, age, and obesity, few studies have delved into the relationship between prediabetes and diabetes specifically with pancreatic steatosis(9). Nevertheless, this topic is gaining more attention over time. For instance, a study by van der Zijl et al. in 2011 found that pancreatic steatosis correlated with fasting blood glucose levels but not with postprandial glucose levels(8). In contrast, our study revealed that pancreatic steatosis was associated with both fasting and postprandial glucose levels, as well as HbA1c levels. We hypothesized that pancreatic steatosis may contribute to damage in pancreatic acinar cells, resulting in reduced insulin secretion, impaired glucose utilization by cells, and subsequently elevated blood glucose levels.

Recent studies have established a connection between pancreatic steatosis and metabolic syndrome, as well as obesity(10, 11). Some research studies have suggested that weight loss and drug therapy may contribute to the reversal of pancreatic steatosis. For instance, a meta-analysis revealed that the normal pancreatic fat percentage was 6.2%, while the prevalence of pancreatic steatosis was 33% in another study involving 12,000 subjects. This meta-analysis also demonstrated that pancreatic steatosis was not significantly correlated with age, gender, or BMI, but it was associated with hypertension, type 2 diabetes, and metabolic syndrome(12).

Our study, mirroring comparable obesity levels in the American population, produced results consistent with those of American studies. For instance, Volk et al. demonstrated a significant increase in the pancreatic fat ratio from 9% in non-obese patients to 17% in obese patients(13).

The relationship between alcohol consumption and steatopancreatitis is not entirely clear. Some studies have suggested that higher alcohol consumption is associated with increased

pancreatic fat content(14). However, in our study, alcohol consumption did not show a statistically significant impact on pancreatic steatosis.

The relationship between dyslipidemia and steatopancreatitis is complex. While some studies have indicated a correlation between pancreatic steatosis and elevated triglyceride levels, our study did not reveal such a relationship(15).

Another intriguing finding in our study was the correlation between HDL levels and pancreatic fat accumulation. Higher HDL levels were associated with lower pancreatic fat accumulation. Previous studies have suggested that HDL may modulate glucose metabolism and play a role in regulating insulin secretion(16, 17). Our results are consistent with a Chinese study that proposed the triglyceride/HDL-C ratio as a robust predictor of insulin resistance(15).

Hyperuricemia, known to be associated with obesity, metabolic syndrome, and type 2 diabetes, has also been linked to hepatic steatosis(18). In recent publications, hyperuricemia has been identified as an independent risk factor for insulin resistance and elevated levels of atherogenic lipids(19). Our study also demonstrated an increase in uric acid levels in both prediabetes and diabetes groups, which correlated with pancreatic steatosis.

Comparing the prediabetes group to the control group, we observed statistically significant fat accumulation in all parts of the pancreas. However, when analysing pancreatic steatosis between the prediabetes and diabetes groups, statistical significance was only observed in the pancreatic head and tail. This suggests that pancreatic steatosis may not solely initiate with diabetes but also exists at prediabetes stages. The presence of pancreatic steatosis in the prediabetes phase may be indicative of its potential role in diabetes.

Conclusion

Our study investigated pancreatic steatosis and its relationship with metabolic parameters in a case population. The findings suggest that pancreatic steatosis is also present in the prediabetes phase, implying that fat accumulation in the pancreas may contribute to the diabetes process and impaired metabolic parameters. However, our study has several limitations, including its retrospective design, the absence of oral glucose tolerance tests in the control group, and the use of computed non-contrast-enhanced tomography instead of magnetic resonance imaging for pancreatic steatosis assessment. Additionally, the predominance of males in the study population may have influenced the results. Further

research is needed to elucidate the causal relationship between pancreatic steatosis and diabetes mellitus and to explore potential therapeutic interventions targeting this mechanism.

Table 1: Clinical and Demographic findings of study population

Variables	Control (n=103)	Prediabetes (n=102)	Diabetes (n=109)	*p value*
Age (year)	50.2±17.4	57.6±13.3	61.3±11.7	*0.001*
Sex (M/F)	65/38	62/47	68/34	*0.33*
BMI (kg/m^2)	23,98	26,95	28,44	*0.001*
Smoking status	56	54	51	*0.74*
Alcohol	24	23	25	*0.83*

Table 2: Laboratory findings of study population

Variables	Control (n=103)	Prediabetes (n=102)	Diabetes (n=109)	*p value*
Urea (mg/dl)	40.3±21.5	40.4±18.4	67.5±46.7	*0.001*
Total bilirubin (mg/dl)	0.77±0.56	0.61±0.31	0.61±0.50	*0.02*

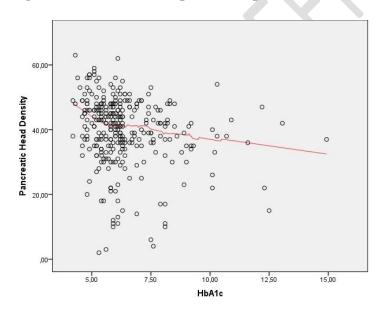|			
Creatinine (mg/dl)	0.97±0.42	0.98±0.36	1.65±1.28	*0.001*
Fasting blood glucose (mg/dl)	83.8±7.9	106.1±8.57	157.9±39.8	*0.001*
Postprandial blood glucose (mg/dl)	105.04±14.2	143.5±22.9	220.3±76.09	*0.001*
HbA1c %	5.10±0.35	6.19±0.2	8.04±1.63	*0.001*
ALT (u/lt)	23.34±13.6	23.5±14.6	23.9±18.4	*0.96*
AST (u/lt)	24.9±25.03	24.8±19.1	34.1±60.7	*0.14*
GGT (u/lt)	41.7±64.4	34.8±36.4	62.08±70.6	*0.003*
ALP (u/lt)	95.7±47.9	93.3±43.3	114.9±70.9	*0.009*
Hemoglobin (g/dl)	12.8±2.48	12.9±1.84	12.05±2.3	*0.01*
Direct bilirubin (mg/dl)	0.27±0.28	0.21±0.22	0.22±0.38	*0.39*
GFR (ml/min)	91.25±27.48	82.4±24.1	60.2±32.3	*0.001*
Uric acid (mg/dl)	5.75±1.97	5.6±1.64	6.7±2.36	*0.001*
INR	1.09±0.18	1.09±0.27	1.25±0.75	*0.017*
Albumin (g/dl)	4.19±0.71	4.16±0.57	3.9±0.74	*0.01*
HDL (mg/dl)	46.2±16.1	42.03±11.3	38.8±11.4	*0.001*
Triglyceride (mg/dl)	115.4±41.6	142.02±60.9	192.4±123.6	*0.001*
LDL (mg/dl)	93.2±25.5	105.0±34.08	106.4±35.1	*0.005*

Total cholesterol (mg/dl)	159.6±34.8	172.59±44.4	178.6±46.3	*0.005*

Abbreviations: ALT: alanine transaminase, AST: aspartate transaminase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase, GFR: glomerular filtration rate, INR: international normalized ratio, HDL: high density lipoprotein, LDL: low density lipoprotein

Table 3: Measurement of pancreas and spleen densities in Hounsfield unit

Variables	Control (n=103)	Prediabetes (n=102)	Diabetes (n=109)	*p value*
Spleen	50.6±5.04	49.4±4.76	48.7±4.96	*0.024*
Pancreatic Head	42.6±9.61	39.1±11.2	37.3±10.26	*0.001*
Pancreatic body	43.87±9.03	39.69±10.08	38.5±8.69	*0.001*
Pancreatic tail	44.0±8.80	40.7±9.27	39.1±8.58	*0.001*

Figure 1: The relationship between pancreatic head density and HbA1c level

Ethics Committee Approval: This study was approved by the local ethics committee. (Date: 03.10.2019, Number: E-19-071, Ankara City Hospital)

Ethical implications: This manuscript does not have any ethical implications in its methodology or results that the reader should consider.

Sources of the tables and figures: They are self-made.

References

1.   Prasad MK, Mohandas S, Ramkumar KM. Dysfunctions, molecular mechanisms, and therapeutic strategies of pancreatic β-cells in diabetes. Apoptosis. 2023;28(7-8):958-76.

2.   Mahdipour E, Azizian M, Mirhafez SR, Ganjali S, Shoeibi S, Nematy M, et al. Relationship between serum pro-and anti-inflammatory cytokine and growth factor concentrations with the age and gender adjusted prevalence of diabetes and pre-diabetes. International Journal of Diabetes in Developing Countries. 2017;37:313-9.

3.   Olsen TS. Lipomatosis of the pancreas in autopsy material and its relation to age and overweight. Acta Pathol Microbiol Scand A. 1978;86a(5):367-73.

4.   Zhou J, Li ML, Zhang DD, Lin HY, Dai XH, Sun XL, et al. The correlation between pancreatic steatosis and metabolic syndrome in a Chinese population. Pancreatology. 2016;16(4):578-83.

5.   Berger Z, Orellana F, Cocio R, Torres F, Simian D, Araneda G, et al. Pancreatic steatosis: A frequent finding in a Chilean population. Rev Gastroenterol Mex (Engl Ed). 2023;88(2):118-24.

6.   Gerst F, Wagner R, Oquendo MB, Siegel-Axel D, Fritsche A, Heni M, et al. What role do fat cells play in pancreatic tissue? Mol Metab. 2019;25:1-10.

7.   Lee JS, Kim SH, Jun DW, Han JH, Jang EC, Park JY, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroenterol. 2009;15(15):1869-75.

8.   van der Zijl NJ, Goossens GH, Moors CC, van Raalte DH, Muskiet MH, Pouwels PJ, et al. Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on β-cell function in individuals with impaired glucose metabolism. J Clin Endocrinol Metab. 2011;96(2):459-67.

9.   Jia DM, Fukumitsu KI, Tabaru A, Akiyama T, Otsuki M. Troglitazone stimulates pancreatic growth in congenitally CCK-A receptor-deficient OLETF rats. Am J Physiol Regul Integr Comp Physiol. 2001;280(5):R1332-40.

10.   Sezgin O, Yaraş S, Özdoğan O. Pancreatic Steatosis Is Associated with Both Metabolic Syndrome and Pancreatic Stiffness Detected by Ultrasound Elastography. Dig Dis Sci. 2022;67(1):293-304.

11.   Sunouchi M, Inaishi J, Shimizu-Hirota R, Saisho Y, Hayashi K, Takaishi H, et al. Longitudinal changes in pancreatic volume and pancreatic fat with weight gain in Japanese without diabetes: An analysis using health check-up data. Metabol Open. 2023;19:100250.

12.   Singh RG, Yoon HD, Wu LM, Lu J, Plank LD, Petrov MS. Ectopic fat accumulation in the pancreas and its clinical relevance: A systematic review, meta-analysis, and meta-regression. Metabolism. 2017;69:1-13.

13.   Volk BW, Wellmann KF. Quantitative studies of the islets of nondiabetic patients. The diabetic pancreas: Springer; 1985. p. 117-25.

14.   Uygun A, Kadayifci A, Demirci H, Saglam M, Sakin YS, Ozturk K, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis. Eur J Intern Med. 2015;26(1):37-41.

15.   Zhou M, Zhu L, Cui X, Feng L, Zhao X, He S, et al. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance but not of β cell function in a Chinese population with different glucose tolerance status. Lipids Health Dis. 2016;15:104.

16.   Drew BG, Duffy SJ, Formosa MF, Natoli AK, Henstridge DC, Penfold SA, et al. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. Circulation. 2009;119(15):2103-11.

17.   von Eckardstein A, Widmann C. High-density lipoprotein, beta cells, and diabetes Cardiovasc Res. 2014;103(3):384-94.

18.   Wan X, Xu C, Lin Y, Lu C, Li D, Sang J, et al. Uric acid regulates hepatic steatosis and insulin resistance through the NLRP3 inflammasome-dependent mechanism. J Hepatol. 2016;64(4):925-32.
19.   King C, Lanaspa MA, Jensen T, Tolan DR, Sánchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol. 2018;192:88-102.