Pancreatic Lipid Deposits: Is There a Connection toPre-diabetesandDiabetesMellitus?

ABSTRACT

Objective: Thestudyfocused on elucidatingthe presence of pancreaticsteatosis in pre-diabetesanddiabetesmellitusalongwithinvestigatingthecorrelationbetweenpancreaticsteatosisand metabolicparameters.

Methods: Thisresearchinvolved 314 patientswhosoughttreatment at internalmedicineoutpatientandinpatientclinicsfrom April 2022to May 2023. Patientswhounderwentnon-enhanced abdominal computedtomographyforanyreasonwereincluded in thestudy. Thepatientswerecategorizedintothreegroups: healthycontrols(n=103), diabetesindividuals(n=109), andprediabetesindividuals(n=102).

Results:

Thestudyaimedtoexploretherelationshipbetweenpancreaticsteatosisandmetabolicparameters. Thefindingsrevealedthat HDL level, albumin, andglomerularfiltration rate (GFR) showed a positivecorrelationwithpancreaticdensity, indicating a lowerdegree of steatosis in thepancreatictissue. Conversely, patientswithhigherlevels of HbA1c, uricacid, bloodglucoselevels, body massindex, INR exhibited a higherdegree of pancreaticsteatosis.

Furthermore, theresearchidentifiedthe presence of pancreaticsteatosis in prediabetespatients. Therewasnosignificantdifference in pancreaticsteatosisbetweenprediabetesanddiabetespatients, suggestingthattheirpancreaticdensitieswerestatisticallysimilar(p=0,08).

Conclusion: Ourstudyinvestigatedpancreaticsteatosis in diabetesandpre-diabetespatients, anditsrelationshipwithmetabolicparameters.Thefindingssuggestthatpancreaticsteatosis is alsopresent in theprediabetesphaseand it has a correlationwithmetabolicparametersseen in diabetesprocess.

Keywords: Diabetesmellitus, prediabeticstate, steatosis, hemoglobin A1c protein

Introduction

Type 2 diabetesmellitus is characterizedby a gradualdecline in pancreatic beta cells, resulting in hyperglycemia. Currently, diabetesmellitus is regarded as equivalenttocardiovasculardisease. However, theprecisecause of beta cellloss in type 2

diabetesmellitusremainselusive. Theprimarymechanismcontributingtotheobserved insulin resistance in type 2 diabetesmellitus is believedto be a reduction in insulin secretionfrompancreatic beta cells. Thisdamageto beta cells is hypothesizedtostemfrommetabolicstressandinflammation(1, 2).

Prediabetes is acknowledged as an intermediatephasebetween normal bloodglucoselevelsandtheelevatedglucoselevelsobserved in type 2 diabetesmellitus. Inthisstage, individualsmaydemonstrateimpairedfastingbloodglucoseand/orimpairedglucosetolerance.

Pancreaticsteatosisreferstotheaccumulation of fat in pancreatictissue, leadingtothereplacement of the normal pancreasparenchyma(3). Thiscondition can be inducedbyvariousfactors, including viral infections, pancreatitis, neoplasms, diabetesmellitus, aging, andhypercholesterolemia(4). Nevertheless, theassociationbetweenpancreaticsteatosisandthepathophysiologicalmechanisms of diabetesmellitus, as well as itsinfluence on theprogression of diabetesmellitus, remainsunclear(5).There is a scarcity of studiesexaminingtheconnectionbetweenprediabetes, diabetes, andpancreaticsteatosis. Someresearchersproposethat insulin resistance is an outcome of a fattypancreas, whileothersmaintainopposingviews(6).

Theobjective of thementionedstudy is toinvestigatethecorrelationbetween a fattypancreasandmetabolicparameters. Through an exploration of therelationshipbetweenpancreaticsteatosisandpancreatictissuedamage, weaimtogaininsightsintoits role in thedevelopment of diabetesmellitus.

MaterialsandMethods

This is a cross-sectionalretrospectiveresearchstudy. The data of patientsadmittedtointernalmedicineoutpatientandinpatientclinicsbetween April 2022and May 2023werecollectedfromthedatabases. Thestudycomprisedthreegroups: thecontrolgroupincludedpatientswithfastingbloodglucoselevelsbelow 100 mg/dl, theprediabetesgroupincludedpatientswithfastingbloodglucoselevelsbetween 100-126 mg/dl, andthediabetesgroupincludedpatientswithbloodglucoselevels>126 mg/dl.

Forallgroups, patientswho had undergone abdominal non-enhancedcomputedtomographyforanyreasonwereincluded in theresearch. A total of 314

participants (195 male, 119 female), aged 18 yearsandolder, wereincluded in ourproject. Participantswereselectedrandomlybased on theiradmissiondate.

Patientsmeetingthefollowingcriteriawereexcludedfromthestudy: age<18 or>80 yearsold, nephrotic-levelproteinuria, intake of antioxidantand vitamin supplements, chronickidneydiseasestage ≥3, pancreasneoplasm (primaryormetastatic), history of pancreatitis, andhistory of pancreassurgery.

Thisstudyreceivedapprovalfromthelocalethicscommitteeandvariousdemographic data andlaboratoryparameters of thepatientswereretrospectivelycollectedandexaminedfromavailablemedicalrecordsandthehospitaldatabasesystem. Demographic data includedage, sex, BMI (body massindex), alcoholconsumption, andcigarettehistory. Thecollectedandanalysedlaboratoryparameterscomprised GFR (glomerularfiltration rate), creatinine, alanineaminotransferase (ALT), aspartateaminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), INR (internationalnormalizedratio), HbA1c (glycated hemoglobin), completebloodcount, uricacid, bilirubinlevels, total lipid profile, fastingbloodglucoselevels, and post-OGTT (oral glucosetolerance test) levels. Additionally, serum albuminlevelswerealsoconsidered.Obesitywasdefined as having a BMI equaltoorgreaterthan 30.

Inthestudy, radiologicimageswereretrievedfrom a database, andtheseimageswereacquiredusing 128-sliced tomography (GE Healthcare, Chicago, USA). Contrast-enhancedtomographyimageswereexcludedfromthestudy. The abdominal computedimagesweresubsequentlyscrutinizedby two differentradiologyspecialistssimultaneously. Thesespecialistswereblindedtothemedicalstatus of thesubjectstomaintainobjectivity.Thefindings of theirexaminationwererecordedanddemonstratedagreement.

Thedensities of theliver, pancreas, andspleenparenchymawerequantified in HounsfieldUnits (HU) utilizing a 0.5 cm^2 ellipticalregion of interest (ROI). Liverdensitymeasurementsinvolvedseparateassessments of therightlobe, leftlobe, andcaudatelobe. Inthecase of spleendensitycalculations, theupper, middle, andlowerpartswereexamined, andthemean of thesemeasurementswasrecorded. Thismeticulousapproachtoimageanalysisensuredpreciseanddependableassessment of theradiologic data in thestudy.

Statistical analysis

Allstatisticalanalyseswereconductedusing SPSS software, version 21.0 (SPSS, Inc., Chicago, IL, USA). Normallydistributedcontinuousvariableswerepresented as means ± standarddeviation (SD). Forcontinuousvariablesthatdid not follow a normal distribution, thecomparisonbetweengroupswasperformedusingtheKruskal-Wallis test. TheStudent's t-test wasemployedtoassessdifferencesbetweenthepancreaticsteatosisandnon-pancreaticsteatosisgroups. Binarylogisticregressionwasusedtoevaluateindependent risk factorsassociatedwithpancreaticsteatosis. Therelationshipbetweenpancreaticsteatosisandmetabolicparameterswasdeterminedusingthechi-square test. A p-value of lessthan 0.05 wasconsideredstatisticallysignificant.

Results

Theaverageages of thecontrol, prediabetes, anddiabetesgroupswere 50.2 ± 17.4, 57.6 ± 13.3, and 61.3 ± 11.7 years, respectively. Thediabetesgroupwassignificantlyolderthantheothergroups ($p < 0.01$). Themeanweightwas72.2 kg in thecontrolgroup, 77.9 kg in theprediabetesgroup, and 81.8 kg in thediabetesgroup. Bothprediabetesanddiabetespatients had a higherweightcomparedtothecontrolgroup ($p < 0.01$). Therewerenosignificantdifferences in alcoholconsumptionandsmokingstatusamongthethreegroups. Detailedclinical data of thepatientsarepresented in Table 1.

Interms of laboratoryfindings, thediabetesgroupexhibitedelevatedcreatininelevels (1.65 ± 1.28 mg/dl) in comparisontothecontrol (0.97 ± 0.42 mg/dl) andprediabetes (0.98 ± 0.36 mg/dl) groups ($p < 0.05$). Ureaanduricacidlevelswerealsohigher in thediabetesgroup ($p < 0.05$). Fastingbloodglucoseand 2-hour postprandialglucoselevelsweresignificantlyelevated in thediabetesgroup ($p < 0.05$). GFR levelswerelower in thediabetesandprediabetesgroupscomparedtothecontrolgroup ($p < 0.05$). Detailedbiochemicalresults of thepatientsarepresented in Table 2.

Pancreaticfataccumulationwasobservedto be higher in thepancreaticheadandlower in thepancreatictailregion. Pancreatictissuedensitydecreased, andpancreaticfatdepositionincreased in thediabetesgroupacrossallparts of thepancreas ($p < 0.001$). Themeasurements of pancreasdensities in HounsfieldUnits (HU) arepresented in Table 3.

Toinvestigatetheeffects of clinicalvariables on pancreaticfataccumulation, logisticregressionanalysiswasconducted. The data wereanalysed in subgroups, such as pancreaticheadfataccumulationandpancreatic body andtailfatgroup (N=314). ItwasdeterminedthatBMI > 30, HDL level< 60 mg/dl, uricacidlevel> 7 mg/dl, albumin< 3.4 g/dl, GFR < 89 ml/dl/1.73m², and HbA1c (refertoFigure 1) werestatisticallyassociatedwithpancreaticsteatosis ($p < 0.05$). It is alsoobservedthattherewas a correlation of pancreaticheaddensitywith lipid levelsalongwith HbA1c($p < 0.05$).

Discussion

Thenatureandclinicalimplications of pancreaticsteatosis, orpancreaticfataccumulation, continueto be a subject of debate. Somestudiessuggestthatpancreaticsteatosismayleadtoinflammation of thepancreasanddegeneration of acinarcells(7). Additionally, it has beensuggestedthatfat in thepancreasmayfunction as an endocrine organ, secretingadipocytokinesthatpromotemacrophageinfiltration(8). Whilepreviousresearch has linkedpancreaticsteatosiswithdiabetes, age, andobesity, fewstudieshavedelvedintotherelationshipbetweenprediabetesanddiabetesspecificallywithpancreaticsteatosis(9). Nevertheless, thistopic is gainingmoreattentionover time. Forinstance, a studybyvan der Zijl et al. in 2011 foundthatpancreaticsteatosiscorrelatedwithfastingbloodglucoselevels but not withpostprandialglucoselevels(8). Incontrast, ourstudyrevealedthatpancreaticsteatosiswasassociatedwithbothfastingandpostprandialglucoselevels, as well as HbA1c levels. Wehypothesizedthatpancreaticsteatosismaycontributetodamage in pancreaticacinarcells, resulting in reduced insulin secretion, impairedglucoseutilizationbycells, andsubsequentlyelevatedbloodglucoselevels.

Recentstudieshaveestablished a connectionbetweenpancreaticsteatosisandmetabolicsyndrome, as well as obesity(10, 11). Someresearchstudieshavesuggestedthatweightlossanddrugtherapymaycontributetothereversal of pancreaticsteatosis(12).Forinstance, a meta-analysisrevealedthatthe normal pancreaticfatpercentagewas 6.2%, whiletheprevalence of pancreaticsteatosiswas 33% in anotherstudyinvolving 12,000 subjects. This meta-analysisalsodemonstratedthatpancreaticsteatosiswas not significantlycorrelatedwithage,

gender, or BMI, but it wasassociatedwithhypertension, type 2 diabetes, andmetabolicsyndrome(13).

Ourstudy, mirroringcomparableobesitylevels in theAmericanpopulation, producedresultsconsistentwiththose of Americanstudies. Forinstance, Volk et al. demonstrated a significantincrease in thepancreaticfatratiofrom 9% in non-obesepatientsto 17% in obesepatients(14).

Therelationshipbetweenalcoholconsumptionandsteatopancreatitis is not entirelyclear. Somestudieshavesuggestedthathigheralcoholconsumption is associatedwithincreasedpancreaticfatcontent(15, 16).However, in ourstudy, alcoholconsumptiondid not show a statisticallysignificantimpact on pancreaticsteatosis.

Therelationshipbetweendyslipidemiaandsteatopancreatitis is complex. Whilesomestudieshaveindicated a correlationbetweenpancreaticsteatosisandelevatedtriglyceridelevels(17),ourstudydid not revealsuch a relationship.

Anotherintriguingfinding in ourstudywasthecorrelationbetween HDL levelsandpancreaticfataccumulation. Higher HDL levelswereassociatedwithlowerpancreaticfataccumulation. Previousstudieshavesuggestedthat HDL maymodulateglucosemetabolismandplay a role in regulating insulin secretion(18, 19). Ourresultsareconsistentwith a Chinesestudythatproposedthetriglyceride/HDL-C ratio as a robustpredictor of insulin resistance(17).

Hyperuricemia, knownto be associatedwithobesity, metabolicsyndrome, andtype 2 diabetes, has alsobeenlinkedtohepaticsteatosis(20). Inrecentpublications, hyperuricemia has beenidentified as an independent risk factorfor insulin resistanceandelevatedlevels of atherogeniclipids(21). Ourstudyalsodemonstrated an increase in uricacidlevels in bothprediabetesanddiabetesgroups, whichcorrelatedwithpancreaticsteatosis.

Comparingtheprediabetesgrouptothecontrolgroup, weobservedstatisticallysignificantfataccumulation in allparts of thepancreas. However, whenanalysingpancreaticsteatosisbetweentheprediabetesanddiabetesgroups, statisticalsignificancewasonlyobserved in thepancreaticheadandtail. Thissuggeststhatpancreaticsteatosismay not solelyinitiatewithdiabetes but alsoexists at

prediabetesstages. The presence of pancreaticsteatosis in theprediabetesphasemay be indicative of itspotential role in diabetes.

Inconclusion, ourstudyinvestigatedpancreaticsteatosisanditsrelationshipwithmetabolicparameters in a casepopulation. Thefindingssuggestthatpancreaticsteatosis is alsopresent in theprediabetesphase, implyingthatfataccumulation in thepancreasmaycontributetothediabetesprocessandimpairedmetabolicparameters. However, ourstudy has severallimitations, includingitsretrospectivedesign, theabsence of oral glucosetolerancetests in thecontrolgroup, andtheuse of computednon-contrast-enhancedtomographyinstead of magneticresonanceimagingforpancreaticsteatosisassessment. Additionally, thepredominance of males in thestudypopulationmayhaveinfluencedtheresults. Furtherresearch is neededtoelucidatethecausalrelationshipbetweenpancreaticsteatosisanddiabetesmellitusandtoexplorepotentialtherapeuticinterventionstargetingthismechanism.

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Table 1: ClinicalandDemographicfindings of studypopulation

Variables	**Control (n=103)**	**Prediabetes (n=102)**	**Diabetes (n=109)**	***pvalue***
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*

Smokingstatus	56	54	51	*0.74*
Alcohol	24	23	25	*0.83*

Key: thesymbol ± standarddeviationindicates how far a valuedeviatesfromthemeanvalue.

Table 2: Laboratoryfindings of studypopulation

Variables	**Control (n=103)**	**Prediabetes (n=102)**	**Diabetes (n=109)**	***pvalue***
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*
Fastingbloodglucose (mg/dl)	83.8±7.9	106.1±8.57	157.9±39.8	*0.001*
Postprandialbloodglucose (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*

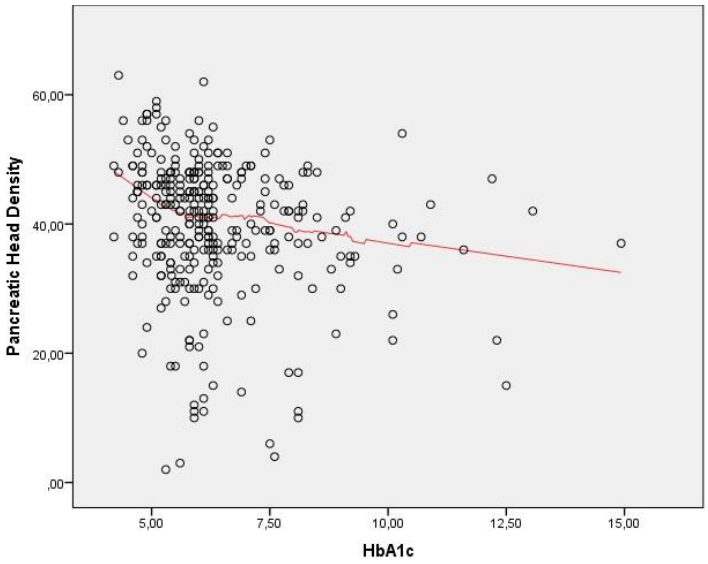
Uricacid (mg/dl)	5.75±1.97	5.6±1.64	6.7±2.36	*0.001*
INR	1.09±0.18	1.09±0.27	1.25±0.75	*0.017*
Albumin (g/dl)	4.19±0.71	4.16±0.57	3.9±0.74	*0.01*
HDL (mg/dl)	46.2±16.1	42.03±11.3	38.8±11.4	*0.001*
Triglyceride (mg/dl)	115.4±41.6	142.02±60.9	192.4±123.6	*0.001*
LDL (mg/dl)	93.2±25.5	105.0±34.08	106.4±35.1	*0.005*
Total cholesterol (mg/dl)	159.6±34.8	172.59±44.4	178.6±46.3	*0.005*

Abbreviations: ALT: alaninetransaminase, AST: aspartatetransaminase, GGT: gamma-glutamyltransferase, ALP: alkaline phosphatase, GFR: glomerularfiltration rate, INR: internationalnormalizedratio, HDL: highdensity lipoprotein, LDL: lowdensity lipoprotein

Table 3: Measurement of pancreasandspleendensities in Hounsfieldunit

Variables	**Control (n=103)**	**Prediabetes (n=102)**	**Diabetes (n=109)**	***pvalue***
Spleen	50.6±5.04	49.4±4.76	48.7±4.96	*0.024*
PancreaticHead	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*
Pancreatictail	44.0±8.80	40.7±9.27	39.1±8.58	*0.001*

Figure 1: Therelationshipbetweenpancreaticheaddensityand HbA1c level



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