HHS Public Access

Author manuscript

Pancreas. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Pancreas. 2022 July 01; 51(6): 586–592. doi:10.1097/MPA.0000000000002080.

Design and Rationale for the Use of Magnetic Resonance Imaging Biomarkers to Predict Diabetes Following Acute Pancreatitis in the *D*iabetes *RE*lated to *A*cute Pancreatitis and Its *M*echanisms (DREAM) Study: From the Type 1 Diabetes in Acute Pancreatitis Consortium (T1DAPC)

Temel Tirkes, MD,
Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

Vernon M. Chinchilli, MD,
Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA

Ulas Bagci, PhD,
Machine & Hybrid Intelligence Lab, Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, Department of Biomedical Engineering, Northwestern University, Chicago, IL, Department of Electrical and Computer Engineering, Northwestern University, Chicago, IL

Jason G. Parker, PhD,
Department of Radiology & Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

Xuandong Zhao, PhD,
Department of Radiology & Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

Anil K. Dasyam, MD,
Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, PA

Nicholas Feranec, MD,
Department of Radiology, AdventHealth, Orlando, FL

Joseph R. Grajo, MD,

Address correspondence to: Temel Tirkes, MD, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 550 N. University Blvd. Suite 0663, Indianapolis, IN, 46202 (atirkes@iupui.edu). Tele: 317-944-1837, Fax: 317-944-1848. D.L.C. is currently with the Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, KY

Conflicts of Interest:
Besides the funding support from NIH listed about, C.E.F. receives consultant fee or honorarium from Nestle HealthCare Nutrition, Inc., Parexel International Corp and Medialis, Ltd. M.D.B. is an advisory board member of Insulet and receives research support from Dexcom and Viacyte. S.J.P. owns stock options of Avenzoar Pharmaceuticals, Phyteau, and Lucid Sciences. W.G.P. is a consultant for Abbvie. B.S. is a consultant for Francis Medical and Botimage. T.T. receives royalties from Springer Nature. J.R.G. receives royalties from Elsevier, Inc. D.K.A. receives royalties from McGraw-Hill. R.E.P. is consultant for Bayer AG; Corcept Therapeutics Incorporated; Dexcom; Gasherbrum Bio, Inc.; Hanmi Pharmaceutical Co.; Hengrui (USA) Ltd.; Merck; Novo Nordisk; Pfizer; Rivus Pharmaceuticals, Inc.; Sanofi; Scohia Pharma Inc.; Sun Pharmaceutical Industries and receives speaker fees from Novo Nordisk. The rest of the authors declare no conflict of interest.

Department of Radiology, College of Medicine, University of Florida, Gainesville, FL

Zarine K. Shah, MD,
Department of Radiology, Ohio State University Wexner Medical Center, Columbus, OH

Peter D. Poullos, MD,
Department of Radiology, Stanford University School of Medicine, Stanford, CA, Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA

Benjamin Spilseth, MD, MBA,
Department of Radiology, University of Minnesota Medical School, Minneapolis, MN

Atif Zaheer, MD,
Department of Radiology, Johns Hopkins Medicine, Baltimore, MD

Karen L. Xie, DO,
Department of Radiology, University of Illinois at Chicago, Chicago, IL

Ashley M. Wachsman, MD,
Department of Radiology, Cedars Sinai Medical Center, Los Angeles, CA

Martha Campbell-Thompson, DVM, PhD,
Department of Pathology, Immunology, and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, FL

Darwin L. Conwell, MD, MSc,
Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH

Evan L. Fogel, MD,
Lehman, Bucksot and Sherman Section of Pancreatobiliary Endoscopy, Indiana University School of Medicine, Indianapolis, IN

Christopher E. Forsmark, MD,
Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, College of Medicine, University of Florida, Gainesville, FL

Phil A. Hart, MD,
Division of Gastroenterology, Hepatology & Nutrition, Department of Medicine, Ohio State University Wexner Medical Center, Columbus, OH

Stephen J. Pandol, MD,
Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

Walter G. Park, MD,
Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University Medical Center, Stanford, CA

Richard E. Pratley, MD,
AdventHealth Translational Research Institute, Orlando, FL

Cemal Yazici, MD, MS,

Division of Gastroenterology and Hepatology, Department of Medicine, University of Illinois at Chicago, Chicago, IL

Maren R. Laughlin, PhD,
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Dana K. Andersen, MD,
Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Jose Serrano, MD, PhD,
Liver, Pancreas and Gastrointestinal Neuroendocrinology Programs, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD

Melena D. Bellin, MD,
Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN, Department of Surgery, University of Minnesota Medical School, Minneapolis, MN

Dhiraj Yadav, MD, MPH
Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, PA

Type 1 Diabetes in Acute Pancreatitis Consortium

Abstract

This core component of the *D*iabetes *RE*lated to *A*cute pancreatitis and its *M*echanisms (DREAM) study will examine the hypothesis that advanced magnetic resonance imaging (MRI) techniques can reflect underlying pathophysiologic changes and provide imaging biomarkers that predict diabetes mellitus (DM) following acute pancreatitis (AP). A subset of participants in the DREAM study will enroll and undergo serial MRI examinations using a specific research protocol. We aim to differentiate at-risk individuals from those who remain euglycemic by identifying parenchymal features following AP. Performing longitudinal MRI will enable us to observe and understand the natural history of post-AP DM. We will compare MRI parameters obtained by interrogating tissue properties in euglycemic, prediabetic and incident diabetes subjects and correlate them with metabolic, genetic, and immunological phenotypes. Differentiating imaging parameters will be combined to develop a quantitative composite risk score. This composite risk score will potentially have the ability to monitor the risk of DM in clinical practice or trials. We will use artificial intelligence, specifically deep learning, algorithms to optimize the predictive ability of MRI. In addition to the research MRI, the DREAM study will also correlate clinical computerized tomography and MRI scans with DM development.

Keywords

pancreas; MRI; CT; volume; perfusion; artificial intelligence

INTRODUCTION

According to recent reports, pancreatogenic diabetes mellitus (DM), a known complication of acute pancreatitis (AP), may occur more frequently than previously recognized.[1] However, there are limited prospective data from well-phenotyped patients following AP to confirm these retrospective data. The Type 1 Diabetes in Acute Pancreatitis Consortium (T1DAPC) was recently formed to fill this knowledge gap.[2] The primary longitudinal study of the T1DAPC is the *D*iabetes *RE*lated to *A*cute pancreatitis and its *M*echanisms (DREAM) study, which is described elsewhere in this issue. The DREAM study will collect and analyze computed tomography (CT) and magnetic resonance imaging (MRI) scans performed as part of the clinical care of enrolled pancreatitis patients. In addition, we will also conduct research MRI scans in a sub study of DREAM subjects entitled Imaging Morphology of Pancreas in Diabetic Patients Following Acute Pancreatitis (IMMINENT) which is funded separately by the National Institutes of Health (RFA-DK-21-501). The main hypothesis is that MRI can predict the development of prediabetes (pre-DM) or type 1 diabetes mellitus (T1D) and other forms of DM by identifying pathophysiologic changes in the pancreatic parenchyma following AP. We will explore the potential of MRI examinations to differentiate at-risk patients from those who will remain euglycemic. Serial MR examinations will monitor several morphological and pathophysiologic changes. The primary objective is to use several novel MRI techniques to define the natural history of the development of pre-DM and DM in post-AP patients. Secondary objectives include correlating these MRI and artificial intelligence (AI) parameters with the functional, metabolic, genetic, and immunological phenotypes established by the DREAM study.

Background and Rationale

It is well accepted that MRI is superior to CT in demonstrating soft-tissue contrast.[3] Magnetic resonance imaging also offers advanced imaging techniques that can be used to interrogate specific tissue properties, such as dynamic contrast-enhanced (DCE) MRI, intravoxel incoherent motion (IVIM), or diffusion-weighted imaging (DWI). Some MRI-detectable phenomena are thought to be involved in the pathogenesis of AP and DM, whereas others may be the consequence of pancreatic disease.

Previous MRI studies have described altered pancreas size and morphology in patients with T1D, even prior to the onset of clinical DM.[4-6] The dynamics of decline in pancreas volume associated with T1D are uncertain; however, we expect the pancreas to be smaller in patients with new-onset T1D. We will measure pancreas volume both manually and using AI tools. The islets of Langerhans receive a disproportionate share of pancreatic perfusion (10%–20%) given their relative contribution to total pancreatic volume (2%).[7] Glucose is a potent stimulant for islet cell perfusion, resulting in at least a threefold increase in blood flow.[8,9] We will assess innovative MRI parameters of tissue perfusion dynamics using IVIM and DCE MRI to determine whether hypoperfusion of pancreas parenchyma may be a risk marker for pre-DM or DM. Prior studies have reported a higher prevalence of pancreatic fat fraction in patients with type 2 diabetes (T2D) and obesity.[10-12] We will measure the pancreatic fat signal using MRI, and we expect the fat fraction to be higher in the new-onset DM group compared to the control group. It has been postulated that

patients with T1D exhibit exocrine pancreas dysfunction secondary to a lack of insulin and dysregulation of endocrine function.[13,14] Imaging studies have reported a correlation of the T1 signal intensity ratio (SIR) specifically with pancreatic exocrine dysfunction measured by the endoscopic pancreatic function tests.[15,16] Noda et al reported that pancreatic T1 relaxation time is significantly increased with pre-DM individuals and moderately correlates with HbA1c, suggesting that T1 has the potential of being an imaging biomarker for DM.[17] We expect the T1 SIR to be reduced in patients with DM due to the possibility of exocrine dysfunction. Deep learning (DL) is a sub-class of AI wherein layers of neural networks are trained by adjusting parameters; in radiology, it is typically used for detection, segmentation, or classification.[18] We will utilize AI tools, specifically DL algorithms, to automate pancreas and muscle volume measurement and DL algorithms to identify parenchymal changes not visible to the human eye.

MATERIALS AND METHODS

Clinical Imaging and Analysis

Most of the participants in the DREAM study will undergo a cross-sectional examination using standard CT or MRI/MRCP (MR cholangiopancreatography) imaging protocols as part of routine clinical care. Imaging protocols for clinical CT, MRI, and MRCP are developed for the DREAM study; however, we will also utilize any CT or MRI studies performed prior to the participants' enrollment in the DREAM study. Using the data points listed in Table 1, a site radiologist who has completed protocol-specific training will collect data from clinical studies. Completed case report forms and de-identified cross-sectional studies done for qualifying episode will be uploaded to the central data repository at Penn State University.

Research MRI Arm (the IMMINENT Study)

A subgroup of up to 250 participants enrolled in longitudinal follow-up in the DREAM study will undergo longitudinal research MRI scans at 3, 12, 24, and 33 months (Fig. 1). Additionally, we will perform a one-time MRI in participants who were not enrolled in longitudinal research MRI; however, develop new-onset DM. MRIs will be performed at 10 of the T1DAPC clinical centers: Indiana University (Indianapolis, Ind), University of Minnesota (Minneapolis, Minn), Cedars Sinai Medical Center (Los Angeles, Calif), University of Illinois at Chicago (Chicago, Ill), AdventHealth System (Orlando, Fla), University of Florida (Gainesville, Fla), Stanford University (Stanford, Calif), Johns Hopkins University (Baltimore, Md), University of Pittsburgh (Pittsburgh, Pa), and the Ohio State University Wexner Medical Center (Columbus, Ohio).

Statistical Modelling

Based on published data, we estimate that among 250 participants, 34 participants will develop DM, 43 will develop pre-DM, and 148 will remain euglycemic at 12 months (allowing a 10% loss to follow-up) (Fig. 1). We assume the research MRI participants will exhibit the same rate of loss to follow-up (10% within 12 months and 20% within 24 months). We also assume a 5% annual transitional rate (gray arrows) from euglycemia to DM, a 5% transitional rate from euglycemia to pre-DM, and a 5% transitional rate

from pre-DM to DM throughout the study timeline. Given the scarcity of longitudinal imaging studies, our sample size and statistical power calculations are based on Virostko et al,[19] who observed that patients with T1D (not associated with AP) had a pancreas volume 47% smaller than that of euglycemic patients. Specifically, the pancreatic volume index value was 0.69 (standard deviation [SD], 0.37) ml/kg among patients with T1D and 1.2 (SD, 0.35) ml/kg among euglycemic individuals. Based on these index values, we assume the pancreatic volume index will be 0.95 (SD, 0.36) ml/kg among pre-DM patients because pre-DM can be considered a transitional stage between euglycemia and DM. Our application of the Kruskal-Wallis nonparametric analysis of variance shows that there is over 90% statistical power with a two-sided significance level test for comparing the three glycemic groups to the pancreatic volume index. In conjunction with the study protocol, we will incorporate the three-month pancreatic volume index as a regressor in a discrete-time hazards regression model to predict DM incidence. With a sample size of 200 MRI patients at 24 months and a DM incidence of 15%, the precision of the regression model is expressed in terms of a 95% confidence interval of (0.08-0.21) for the DM incidence.

Research MRI Parameters

We will collect several research MRI parameters: three-dimensional (3D) volume using manual segmentation and automated DL algorithms, vascular perfusion using MR perfusion imaging techniques (IVIM and DCE MRI), the pancreatic and liver fat fraction using MRI fat-quantification techniques (Dixon MRI), changes in parenchymal texture using DL algorithms, restriction to diffusion of free water molecules using DWI, T1 mapping and T1-weighted SIR (as a surrogate for pancreatic proteinaceous content), psoas muscle volume (as a surrogate for nutritional status or sarcopenia), and the visceral to subcutaneous fat tissue ratio (as a measure of the pattern of obesity). We will correlate these MRI and AI parameters with the metabolic, genetic, and immunological phenotypes established by the DREAM study.

The Indiana Institute for Biomedical Imaging Sciences will serve as the Core Image Analysis Lab (CIAL) for the research study. The MRI data collection will be performed at the CIAL by experienced MRI research data analysts using dedicated image analysis software. Northwestern University (a satellite site of the Chicago Clinical Center) will serve as the Artificial Intelligence Core Lab (ACL) (Fig. 2). The ACL team will develop DL algorithms to achieve accurate auto segmentation, measurement of gland volume, and subsequent classification of euglycemic, pre-DM, and incident DM cohorts based on glycemic measures collected in the DREAM study.

Research MRI Protocol (the IMMINENT Study)

Magnetic resonance imaging and MRCP will be performed using 3.0T scanners. The generic MRI standard operating procedures shown in Table 2 will be modified and verified for three different hardware vendors (Siemens Medical Solutions USA Inc., Malvern, Pa; GE Healthcare USA, Arlington Heights, Ill; and Phillips Medical Systems, Nashville, Tenn).

Experienced image analysts will independently measure 3D volume, diameter, IVIM metrics (eg, f, D_{fast}, D_{slow}), DCE MRI metrics (e.g., K_{trans} and K_{ve}), the T1 SIR, diffusion

restriction, the T1-weighted water and fat signals, and visceral and subcutaneous adipose tissue volume. All sites will acquire T1 maps using dual flip angle spoiled gradient echo (SPGR) sequence. It is necessary to standardize the quantitative imaging across different institutions and MR manufacturers using a T1 phantom in order to obtain T1 maps as uniform and accurately as possible. Correction for B1 field inhomogeneity will be incorporated. The T1 SIR of the pancreas will be obtained from unenhanced T1-weighted gradient-echo images with fat suppression by dividing the T1-weighted signal intensity of the pancreas by that of the reference organ (spleen, paraspinal muscle, and liver).[16] The DCE MRI will be acquired using a 3D T1-weighted time-resolved MRA sequence with a single 12° flip angle over a predetermined time course.[20] The IVIM sequence will use a free-breathing, single-shot echo-planar imaging design with 4 gradient directions and five b-values: 0, 50, 100, 150, and 400 s/mm^2.[21] Our IVIM sequence will use simultaneous multi-slice acquisition simultaneous multi-slice to reduce scan time.[22] A propriety post-processing software will be used to model and quantify DCE MRI and IVIM image sets. Dynamic contrast-enhanced MRI processing will begin with generating a T1 map from variable flip angle precontrast T1 data using the classic steady-state, dual-angle linear regression model with corrections for B1 inhomogeneity using two-dimensional double angle spin echo EPI.[23] An arterial input function will be measured by placing a region of interest on the abdominal aorta. The ACL team will simultaneously perform 3D segmentation of the pancreas and then classify study groups based on conventional radiomics/texture analysis and advanced classification with DL algorithms. The Dixon MRI technique can separate the water and fat signals and create fat-only and water-only image sets of the pancreas.[24] The pancreatic fat fraction will be calculated by taking the ratio of the signal from fat-only and water-only images. Visceral and subcutaneous spaces will be manually outlined, and volume will be measured using image analysis software. We will apply a fat-segmentation algorithm to automate this process using AI and will measure its success.

Patient Safety and Confidentiality

The MRI scans will be performed under the supervision of an experienced MRI technologist and/or radiology nurse (per practice guidelines at each of the T1DAPC centers). Participants will be screened to confirm that they have none of the contraindications listed in Table 3, have their vital signs documented before and after imaging, and be constantly supervised by a radiology technologist. Per the DREAM study protocol, all serious adverse events that occur within 48 hours following the completion of an MRI scan will be documented and reported. Exposure to high magnetic fields may result in (1) heart rate and rhythm changes (which will be monitored via MR-compatible pulse oximetry or MR-compatible EKG), (2) dizziness, (3) minor nerve stimulation effects, such as muscle twitches and tingling sensations, (4) nausea and vomiting, (5) transient detection of flashes of light, (6) claustrophobia, (7) localized heating of the body, particularly near metal structures, and (8) the displacement of a metallic implant or foreign object in the body by the strong magnetic field. An X-ray of the relevant parts of the body may be performed to determine whether metal objects are present prior to the MRI.

Patient confidentially will be ensured through secure processes, such as the DREAM unique ID, that do not expose protected patient data to public disclosure. A secure image-storage

server will be established at the CIAL to store the MRI studies. User access is highly restricted because only the secure file transfer protocol (SFTP) server will operate in a jailed environment within the Indiana University cluster of servers. The study server is HIPAA (Health Insurance Portability and Accountability Act) compliant and will be situated behind network firewalls. The SFTP server will be set up to restrict access to fixed internet provider numbers; therefore, only the designated locations will have access. In addition, the study-site users will use the RSA-4096-bit key to authenticate to the SFTP server, ensuring that user credentials cannot be intercepted. Once connected, centers user will upload their MR images, which will be automatically sent to an anonymizer pipeline. This pipeline will eliminate any secondary capture images, reports, etc. The de-identified images will be sent to the temporary storage server. Access to the de-identified data in this server will be limited to selected individuals. At the end of the image analysis, research MRI scans will be uploaded to the T1DAPC permanent image repository.

Artificial Intelligence Analysis

In this study, we will use existing AI, specifically DL, tools and develop new ones to perform several tasks: measurement of 3D volume, pancreas texture analysis, and assessment of sarcopenia by measuring psoas muscle volume. The ACL team will modify their deep-capsule-based segmentation networks (SegCaps) and apply them to the MR sequences. For volumetric (3D) segmentation, SegCaps' internal mechanism will be used. It will be compared with other pancreas-segmentation baselines that utilize conventional slice-by-slice image segmentation (ie, pseudo-3D), such as U-Net and its variants. We will improve the segmentation algorithms with newly developed theoretical advances (such as attention mechanisms by Transformers) to mimic the shape and appearance differences of the pancreas better than before. We expect that the proprietary software developed by the Northwestern University team will segment the pancreas accurately and enable a quantitative analysis of the pancreas. In addition, conventional and DL-based radiomics/texture analysis and other quantitative MRI marker evaluations will be performed for comparisons and benchmarking.

DISCUSSION

The DREAM study presents a unique opportunity to prospectively monitor MRI biomarkers in the pancreas and relate them directly to imaging, metabolic and immunological markers of DM. This methodology paper describes the design and rationale for using cross-sectional clinical imaging combined with longitudinal research MRI scans to predict DM following AP. Several preliminary studies have suggested that MRI of the pancreas can detect changes associated with the development of DM. In addition to providing anatomical information, MRI offers a rich toolbox of imaging approaches that are sensitive to a large variety of physiologic and metabolic phenomena such as volume, fat and protein content, fibrosis, and blood flow. Based on this evidence, we propose that novel MRI techniques can be used to understand pathophysiology within the pancreatic parenchyma and can offer methods for defining the natural history of DM after AP.[25] These data will be needed to understand the natural history of morphological, functional, and pathophysiological changes that occur before the development of pre-DM and DM. We will correlate several

MR imaging parameters (eg, perfusion metrics, 3D volume, imaging severity of AP, T1 signal, fat fraction, texture differences, etc.) with participant demographics, etiology of AP, clinical severity of AP, and disease outcome (euglycemic, pre-DM vs DM). In addition, we will stratify imaging parameters in different phenotypes, including but not limited to the type of DM (T1D, T2D, or type 3c DM), laboratory (fasting blood glucose, HbA1c), immunologic phenotypes (beta-cell autoantibodies), EPD, alterations in the intestinal microbiome, dietary patterns or hormonal status (insulin secretion, glucagon, and pancreatic polypeptide). This analysis will be performed using statistical analysis and/or DL algorithms where a wide variety of clinical data can be analyzed. Eventually, we plan to develop a quantitative composite risk score based on useful MRI parameters. This noninvasive and practical imaging biomarker may enable monitoring of the evolution of metabolic dysfunction in clinical practice or clinical trials. These approaches may result in noninvasive imaging biomarkers to identify specific properties of the pancreas associated with DM development. The standardization benefit of quantitative MRI techniques allows more accurate comparison across different platforms, therefore permitting a more useful interpretation.

FUNDING

The T1DAP Consortium is funded by the National Institute of Diabetes and Digestive and Kidney Diseases: grants U01DK127384; U01DK127367; U01DK127377; U01DK127392; U01DK127382; U01DK127403; U01DK127404; U01DK127388; U01DK127395; U01DK127378 and U01DK127400. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ABBREVIATIONS

DREAM	Diabetes Related to Acute Pancreatitis and Its Mechanisms
IMMINENT	Imaging Morphology of Pancreas in Diabetic Patients Following Acute Pancreatitis
MRI	Magnetic Resonance Imaging
DCE-MRI	Dynamic contrast-enhanced MRI
IVIM	Intravoxel incoherent motion
DWI	Diffusion-weighted imaging
MRCP	MR cholangiopancreatography
AP	Acute Pancreatitis
Pre-DM	Prediabetes
DM	Diabetes Mellitus
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus

CIAL	Core Image Analysis Lab
ACL	Artificial Intelligence Core Lab
AI	Artificial Intelligence
T1DAPC	Type 1 Diabetes in Acute Pancreatitis Consortium
SIR	Signal Intensity Ratio
EPD	Exocrine Pancreas Dysfunction
CBD	common bile duct
eGFR	estimated glomerular filtration rate
DL	Deep learning
SegCaps	deep capsule-based segmentation networks

REFERENCES

1. Das SL, Singh PP, Phillips AR, et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut. 2014;63:818–831. [PubMed: 23929695]
2. Type 1 Diabetes in Acute Pancreatitis Consortium (T1DAPC). 2021. Available at: http://t1dapc.net. Accessed March 2022.
3. Kransdorf MJ, Murphey MD. Radiologic evaluation of soft-tissue masses: a current perspective. AJR Am J Roentgenol. 2000;175:575–587. [PubMed: 10954433]
4. Sasamori H, Fukui T, Hayashi T, et al. Analysis of pancreatic volume in acute-onset, slowly-progressive and fulminant type 1 diabetes in a Japanese population. J Diabetes Investig. 2018;9:1091–1099.
5. Williams AJ, Thrower SL, Sequeiros IM, et al. Pancreatic volume is reduced in adult patients with recently diagnosed type 1 diabetes. J Clin Endocrinol Metab. 2012;97:E2109–E2113. [PubMed: 22879632]
6. Campbell-Thompson ML, Kaddis JS, Wasserfall C, et al. The influence of type 1 diabetes on pancreatic weight. Diabetologia. 2016;59:217–221. [PubMed: 26358584]
7. Jansson L, Barbu A, Bodin B, et al. Pancreatic islet blood flow and its measurement. Ups J Med Sci. 2016;121:81–95. [PubMed: 27124642]
8. Nyman LR, Ford E, Powers AC, et al. Glucose-dependent blood flow dynamics in murine pancreatic islets in vivo. Am J Physiol Endocrinol Metab. 2010;298:E807–E814. [PubMed: 20071562]
9. Jansson L, Hellerstrom C. Stimulation by glucose of the blood flow to the pancreatic islets of the rat. Diabetologia. 1983;25:45–50. [PubMed: 6350083]
10. Catanzaro R, Cuffari B, Italia A, et al. Exploring the metabolic syndrome: Nonalcoholic fatty pancreas disease. World J Gastroenterol. 2016;22:7660–7675. [PubMed: 27678349]
11. Singh RG, Yoon HD, Wu LM, et al. Ectopic fat accumulation in the pancreas and its clinical relevance: A systematic review, meta-analysis, and meta-regression. Metabolism. 2017;69:1–13. [PubMed: 28285638]
12. Ou HY, Wang CY, Yang YC, et al. The association between nonalcoholic fatty pancreas disease and diabetes. PLoS One. 2013;8:e62561. [PubMed: 23671610]
13. Piciucchi M, Capurso G, Archibugi L, et al. Exocrine pancreatic insufficiency in diabetic patients: prevalence, mechanisms, and treatment. Int J Endocrinol. 2015;2015:595649. [PubMed: 25892991]
14. Giovenzana A, Vecchio F, Cugnata F, et al. Exocrine pancreas function is impaired in adult relatives of patients with type 1 diabetes. Acta Diabetol. 2022;59:473–479. [PubMed: 34782929]

15. Balci NC, Smith A, Momtahen AJ, et al. MRI and S-MRCP findings in patients with suspected chronic pancreatitis: correlation with endoscopic pancreatic function testing (ePFT). J Magn Reson Imaging. 2010;31(3):601–606. [PubMed: 20187202]
16. Tirkes T, Fogel EL, Sherman S, et al. Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. Abdom Radiol (NY). 2017;42:544–551. [PubMed: 27660281]
17. Noda Y, Goshima S, Tsuji Y, et al. Correlation of quantitative pancreatic T1 value and HbA1c value in subjects with normal and impaired glucose tolerance. J Magn Reson Imaging. 2019;49(3):711–718. [PubMed: 30430688]
18. Chartrand G, Cheng PM, Vorontsov E, et al. Deep learning: A primer for radiologists. Radiographics. 2017;37:2113–2131. [PubMed: 29131760]
19. Virostko J, Williams J, Hilmes M, et al. Pancreas volume declines during the first year after diagnosis of type 1 diabetes and exhibits altered diffusion at disease onset. Diabetes Care. 2019;42:248–257. [PubMed: 30552135]
20. Hu R, Yang H, Chen Y, et al. Dynamic contrast-enhanced MRI for measuring pancreatic perfusion in acute pancreatitis: A preliminary study. Acad Radiol. 2019;26:1641–1649. [PubMed: 30885415]
21. Kang KM, Lee JM, Yoon JH, et al. Intravoxel incoherent motion diffusion-weighted MR imaging for characterization of focal pancreatic lesions. Radiology. 2014;270:444–453. [PubMed: 24126370]
22. Boss A, Barth B, Filli L, et al. Simultaneous multi-slice echo planar diffusion weighted imaging of the liver and the pancreas: Optimization of signal-to-noise ratio and acquisition time and application to intravoxel incoherent motion analysis. Eur J Radiol. 2016;85:1948–1955. [PubMed: 27776645]
23. Yoon JH, Lee JM, Kim E, et al. Quantitative liver function analysis: Volumetric T1 mapping with fast multisection B1 inhomogeneity correction in hepatocyte-specific contrast-enhanced liver MR imaging. Radiology. 2017;282:408–417. [PubMed: 27697007]
24. Dixon WT. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging: a modest proposal with tremendous potential. Radiology. 1988;168:566–567. [PubMed: 3393682]
25. Virostko J, Powers AC. Molecular imaging of the pancreas in small animal models. Gastroenterology. 2009;136:407–409. [PubMed: 19105957]

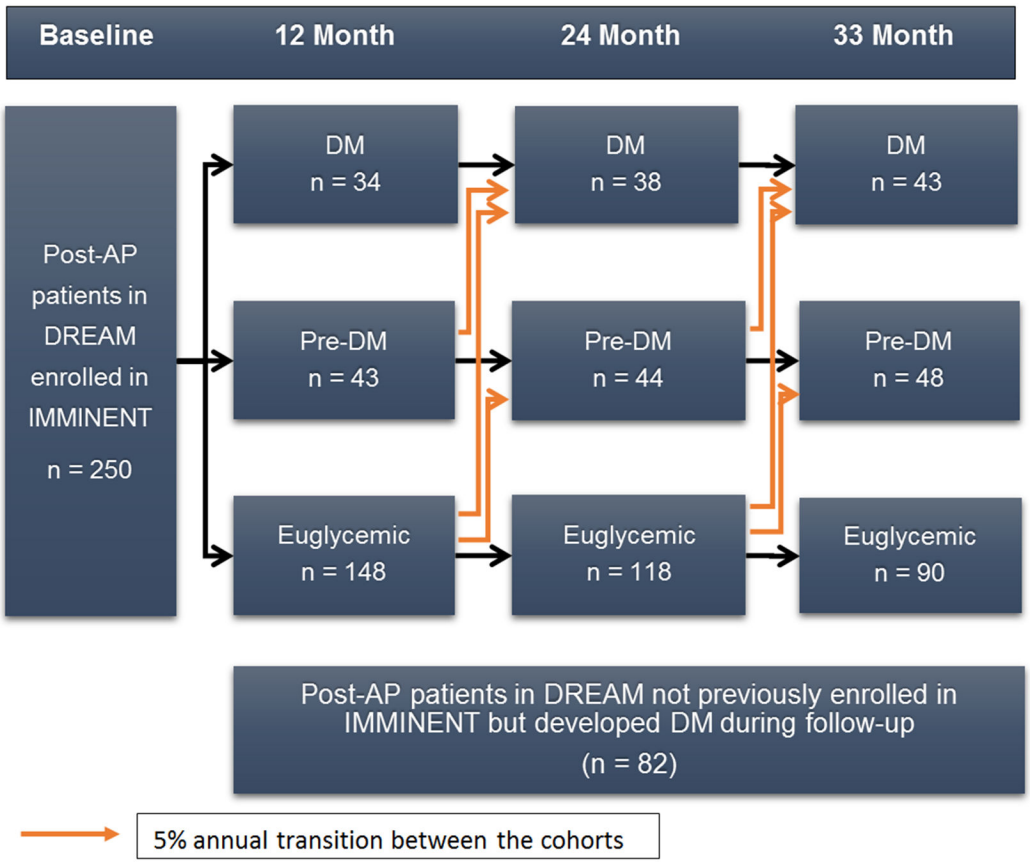

FIGURE 1.
Expected evolution of diabetes status in participants undergoing longitudinal research MRIs in the DREAM study.

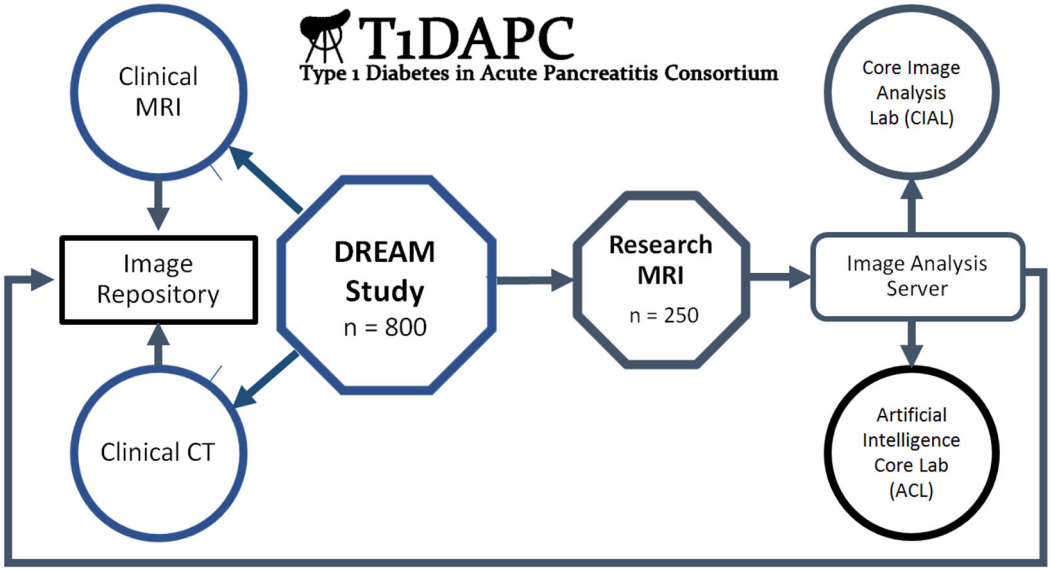

FIGURE 2.
The flow diagram shows research and clinical MRIs and CTs in the DREAM study.

TABLE 1.

Parameters Collected From Clinical CT, MRI, and MRCPs

Findings on CT and/or MRI		
Pancreas diameter, mm	Head, body and tail	
Pancreatic necrosis	Head, body and tail	
Venous thrombosis	**a.**	None
	b.	Splenic
	c.	Portal
	d.	Superior mesenteric vein
Pseudoaneurysm	**a.**	None
	b.	Splenic
	c.	Pancreaticoduodenal
	d.	Gastroduodenal
	e.	Other
Fluid collections	Defined in the revised Atlanta classification	
	a.	Acute peripancreatic fluid collection
	b.	Acute necrotic collection
	c.	Walled off necrosis
	d.	Pseudocyst
Location of fluid collections	**a.**	Lesser sac/perigastric
	b.	Abdominal retro/intraperitoneal
	c.	Pelvis/mediastinum
AP Severity Index	a. Pancreatic inflammation. Give score 0, 1, or 2	
	(0)	Normal pancreas
	(1)	Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
	(2)	Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
	b. Pancreatic necrosis. Give score 0, 1, 2, 4, or 99	
	(0)	None
	(1)	≤30%
	(2)	>30% and ≤50%
	(3)	>50%
	(99)	Cannot assess (non-contrast study)
	c. Extra-pancreatic findings. Give score 0 or 1	
	(0)	None
	(1)	One or more of the following: pleural effusion, ascites, vascular complications, parenchymal complications, involvement of root of mesentery, or gastrointestinal tract)
Findings on MRI and MRCP		
Pancreatic enhancement	Signal intensity on	
	a.	Pre-contrast

	b.	Arterial
	c.	Delayed phases
T1 Signal intensity	**a.**	Pancreas
	b.	Spleen
	c.	Paraspinal muscle
	d.	Liver
Cambridge core	0,1,2,3,4	
CBD diameter	mm	
CBD stone	Yes/No	
Pancreas divisum	Yes/No	

AP indicates acute pancreatitis; CBD, common bile duct.

TABLE 2.

Standard Operating Procedures for IMMINENT MRI and MRCP

I. Before the MRI evaluation

- Verify that patient pass the exclusion criteria.
- Verify the patient fasted for at least 4 hours prior to the study. Fasting includes any sort of liquids, eg, water, coffee, soda. Any type of liquid will obscure the pancreatic ducts.
- Assess the patient's breath-holding capability. If poor, oxygen should be administered.

II. During the MRI evaluation

A. MRI exam guidelines

- All imaging must be performed on a 3T scanner.
- All acquisitions should use a phased-array abdominal coil with a minimum of 8 receive channels. RF transmission will use the built-in body (volume) coil.
- All patients will receive the same contrast agent:
  - **a.** Gadavist® (Gadabutrol, Bayer HealthCare, Whippany, NJ).
- All patients will receive 0.1 mmol/kg (ml), up to 15 ml (1 vial). The contrast dosage should be the same on all patients regardless of the estimated glomerular filtration rate (eGFR).
- The contrast will be injected at a 2 mL/sec rate followed by a saline flush of at least 20 mL.

B. Imaging protocol

MRCP

- FOV ~30 × 35 cm centered over the pancreas
- 2D thick slab MRCP, 40 mm thick, breath hold, 6-8 para-coronal projections to best show the pancreatic duct from different angles
- 3D MRCP: 1 mm respiratory synchronized 3D turbo spin echo sequence, respiratory gated, shallow breathing.

Dixon 2-point fat/water imaging

- Axial T1 weighted 3D 2-point Dixon gradient echo sequence capable of generating water-only and fat-only images in addition to in-phase and op-phase images

Pre-contrast T1-weighted images: 3D gradient echo with fat suppression

- Acquisition plane: Axial
- Sequence: **3D T1: LAVA** (GE), **VIBE** (Siemens), or **THRIVE** (Philips)
- Fat suppression: ON

T1 mapping pre-contrast

- Acquisition plane: axial
- 3D acquisition dual flip angle spoiled gradient echo sequence
- Flip angles to be determined by phantom testing

B1 mapping

- Acquisition plane: axial
- Sequence: sites should use their vendor-provided Fast B1 mapping sequences: satTFL (Siemens), Bloch-Siegert (GE), DREAM (Philips)
- Alternatively, if sites do not have vendor-supplied B1 mapping sequences a 2D SE-EPI may be utilized.
- Slice thickness/gap: 8 mm/8 mm
- TA: ~30 s

Intravoxel incoherent motion (IVIM) imaging and diffusion-weighted imaging (DWI)

- Sequence: Single-shot echo-planar spin-echo with simultaneous multislice (SMS) imaging
- Slice thickness/gap: 3 mm/0.6 mm
- TR/TE/FA: 9700/36
- Acquisition plane: axial free breathing
- Gradient directions: 4
- B-values: 0, 50, 100, 150, 400 s/mm2
- TA: ~3-4 min

Dynamic contrast enhancement (DCE) imaging

- Injected dose weight based at 2 ml/kg
- Injection rate: 2 ml/s flushed by 20 ml of normal saline
- Sequence: 3D T1-weighted time-resolved MRA techniques using radial sampling: TRICKS (GE), 3D-TWIST (Siemens), 4D-TRAK (Philips)
- Slice thickness/gap: 3.5 mm/0 mm
- Acquisition plane: axial
- TA: ~2–3 min

T2-weighted images

- TSE, or a variant of TSE
- Acquisition plane: axial
- Coverage: abdomen only
- Fat suppression: ON

T2-weighted images

- TSE or a variant of TSE
- Acquisition plane: axial and coronal
- Coverage: abdomen only
- Fat suppression: OFF

T1 mapping (post-contrast)

- Acquisition plane: Axial
- Acquisition parameters is same as pre-contrast phase
- Timing: 12-15 minutes after contrast injection

III. After the MRI evaluation

Confirm that the study data form is completed and will be uploaded together with the images. Studies should be electronically transferred using HIPAA compliant secure FTP (SFTP) protocol to the CIAL for post-processing.

FA indicates flip angle; FOV, field of view; GRAPPA, GeneRalized Auto calibrating Partial Parallel Acquisition; HIPAA, Health Insurance Portability and Accountability Act; LAVA, Liver acquisition with volume acceleration; RF, radiofrequency; SE-EPI, spin-echo echo planar imaging; TA, acquisition time; TE: time to echo; THRIVE, T1W High Resolution Isotropic Volume Examination; TR, repetition time; TRAK, Time-Resolved Angiography using Keyhole; TRICKS, Time-resolved imaging of contrast kinetics; TSE, turbo spin echo; TWIST, Time-resolved angiography With Interleaved Stochastic Trajectories; VIBE, Volumetric interpolated breath-hold examination.

TABLE 3.

Exclusion Criteria for Research MRI as Part of the DREAM Study

a. Unwilling or unable to give a written informed consent.
b. Weight ≥350 lbs.
c. History of moderate or severe allergic reaction to a gadolinium-based contrast agent
d. Pregnancy
e. Claustrophobia that is severe enough to necessitate the use of general anesthesia
f. Known estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m2
g. Severe COPD or other chronic lung disease limiting breath-holding for MRI
h. Moderate or large volume ascites (of any etiology)
i. Hemochromatosis
j. Cystic fibrosis
k. Patients with therapeutic body implants, specifically pacemakers, defibrillators, or other implanted electronic devices (eg, pain pump) that are not MRI-compatible, will be excluded. Patients with an IVC filter, body piercing, neurosurgical clip placement, or shrapnel injury will be evaluated individually.

COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IVC, inferior vena cava.