SMART Topic

Imaging Findings of Pancreatic Changes in Type 1 Diabetes

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1. Overview

Type 1 diabetes (T1D) is caused by autoimmune destruction of the pancreatic beta cell. However, the pancreas, the site of T1D pathogenesis, is not directly assessed in T1D. Rather, the disease is diagnosed and monitored by assaying the consequence of the destruction of pancreatic beta cells: lack of insulin production and dysregulation of blood glucose levels. This assessment of disease symptoms, rather than the cause, has important implications for understanding the natural history and treatment of T1D. Dysregulated glucose is thought to occur only after beta cell mass is greatly reduced, putatively due to a functional reserve in this tissue compartment.[1] The autoimmune process underlying T1D can occur years or decades prior to onset of dysglycemia[2], but imaging is not a component of current clinical monitoring in T1D or those at risk. Cross-sectional imaging of the endocrine and exocrine pancreas may provide early predictors of T1D risk and progression. In this review, we summarize current imaging techniques capable of monitoring changes in the pancreas and their potential clinical utility in T1D.

2. Imaging of the Endocrine Pancreas

The ability to non-invasively image pancreatic beta cells would enable direct monitoring of autoimmune destruction in T1D and therapeutic interventions that increase or preserve beta cell mass. However, the small size and scattered distribution of beta cells throughout the pancreas have made them difficult to image in humans. Furthermore, beta cells have no inherent contrast from exocrine pancreas on radiological images. Thus, approaches for imaging pancreatic beta cells in vivo have relied on labeling with exogenous contrast agents that preferentially bind to beta cells.

Positron Emission Tomography (PET) Imaging

PET imaging involves administration of a radiopharmaceutical that binds to a tissue of interest and emits radiation that can be captured by a detector and reconstructed into three-dimensional images. A PET agent for imaging beta cells requires a molecule that binds with high affinity to the beta cell, but not other cell types. Several radiotracers have now been evaluated for beta cell imaging that target different beta cell receptors. Radioligands that target the vesicular monoamine transporter (VMAT) on beta cells have demonstrated lower retention in the pancreas of individuals with T1D.[3] However, high binding of these VMAT-targeted radioligands to a variety of tissues[4] suggests a lack of specificity for beta cells. An alternate approach for beta cell imaging utilizes PET ligands targeting dopamine receptors. These dopamine-directed tracers have also shown lower pancreatic uptake in T1D[5], although concerns about background binding to other cell types persist. The high sensitivity of PET imaging is promising for evaluating small populations of cells, such as pancreatic beta cells. Nonetheless, clinicians must balance sensitivity with the elevated effective radiation dose of PET whole body protocols, comparable to 7.6 years of background exposure.[6] High radiation dose is a key consideration as T1D studies often include pediatric participants and require longitudinal imaging acquisitions to study the natural history of the disease.

Magnetic Resonance Imaging (MRI)

The contrast between different tissues with the MRI modality is governed by differences in relaxation times of protons within the body. The longitudinal relaxation time is a measure of how long it takes an experimentally excited

Abbreviations used in this paper: T1D, Type 1 diabetes; PET, positron emission tomography; VMAT, vesicular monoamine transporter; MRI, magnetic resonance imaging; CT, computed tomography.

Keywords: MRI, PET, CT, ultrasound, volume, islets, beta cells, endocrine, exocrine.

ISSN 2997-2876 (online)
ISSN 2997-2868 (print)
DOI: Http://DOI.org/10.69734/wfpe8y95
Website: www.SMART-MD.org

proton to realign with the magnetic field. Paramagnetic MRI contrast agents have been developed which shorten the longitudinal relaxation time of adjacent molecules and thus appear brighter than unenhanced surrounding tissue. One family of paramagnetic MRI agents contains manganese, which is taken into beta cells through calcium channels during insulin secretion.[7] Manganese contrast agents accumulate at lower concentrations in the pancreas of individuals with T1D and appear to correlate with c-peptide levels.[8] A lack of commercially available manganese agents and concerns about contrast administration safety must be addressed before this technique can be translated to clinical use. An alternate approach is to image the autoimmune process underlying T1D. Gaglia, et al. used magnetic nanoparticles which are internalized by macrophages to assess pancreas inflammation in T1D.[9]

3. Imaging of the Exocrine Pancreas

While T1D has historically been considered a disease of the endocrine pancreas, there is growing appreciation that the exocrine pancreas is also affected. Up to half of individuals diagnosed with T1D have pancreatic exocrine insufficiency based on fecal elastase testing in a research setting.[10] T1D may be associated with a higher risk for developing pancreatitis.[11] These epidemiological findings are supported by autopsy studies that demonstrate exocrine pathology in T1D. For example, pancreatic specimens of individuals with T1D exhibit immune cell infiltration in exocrine tissue[12], acinar atrophy, and ductal fibrosis.[13] The relative time courses of endocrine and exocrine pathology in T1D are unknown; it is unclear if changes in exocrine tissues are a consequence of beta cell loss or a factor contributing to the autoimmune process. A recent National Institutes of Health workshop brought together expertise in endocrine and exocrine pancreas research to better understand interplay between these compartments.[14] Imaging may serve an important purpose in better understanding the crosstalk between the exocrine and endocrine pancreas, building upon the observation that the pancreas is significantly smaller in individuals with T1D.[15] The difference in the size of the pancreas in individuals with T1D (30-40% smaller) exceeds the volume of pancreatic beta cells (1%), thus implicating a loss of exocrine tissue. Multiple imaging approaches can be used to quantify and characterize exocrine pathology in T1D.

Ultrasound

Abdominal ultrasound has been shown to detect a smaller area of the pancreas head and tail in individuals with T1D.[16] Alternatively, ultrasound can measure the diameter of the pancreas head, body, and tail, which were found to be smaller in T1D. The same study also found that pancreas size declined with longer duration of T1D.[17] A technique known as ultrasound elastography can be used to measure the stiffness of the pancreas. Application of ultrasound elastography to cohorts with new-onset and long-standing T1D detected an increase in pancreas stiffness correlating with disease duration.[18] Ultrasound scanners are widespread and relatively inexpensive, making the modality relatively straightforward to implement for pancreas imaging. However, the image quality of ultrasound is poor compared to computed tomography (CT) and MRI, with both limited spatial resolution and frequent obstruction of the pancreas by artifact from bowel gas. Furthermore, pancreatic ultrasound is typically two-dimensional and thus cannot quantify the pancreas volume or assess three-dimensional morphometry.

Computed Tomography (CT)

CT imaging can image the pancreas in three-dimensions with high speed and spatial resolution. These advantages have solidified the role of CT in pancreatic cancer and pancreatitis imaging, where multiplanar reformats can aid detection of tumors, calcifications, and large cysts. Goda et al., used CT to image the pancreas of individuals with T1D and found smaller pancreatic volumes in T1D that correlated with exocrine pancreatic function.[19] Importantly, Goda introduced the concept of normalizing pancreas volume by body surface area to compare individuals with different habitus. The primary limitation of CT for pancreas imaging is exposure to ionizing radiation, similar to PET imaging.

MRI

MRI has excellent soft tissue contrast and is used clinically to image chronic pancreatitis, duct abnormalities, and small pancreatic cystic lesions. MRI can measure the three-dimensional volume of the pancreas and detect a smaller size in T1D with high repeatability of the measurement.[20] MRI has also been utilized to measure pancreas size in individuals at high risk for developing T1D. These studies demonstrate smaller pancreatic dimensions in individuals at risk for T1D.[21] Longitudinal studies of individuals with presymptomatic T1D demonstrate a decline in pancreas volume prior to diagnosis.[22] In addition, MRI can characterize the shape of the pancreas in T1D, which overall demonstrates circumferential pancreas atrophy.[23]

In addition to structural imaging, which delineates size and shape of the pancreas, MRI contrast can be tuned to provide functional information on pancreatic tissue composition. For instance, diffusion-weighted imaging can assay water molecule movement through a tissue voxel. Areas of increased diffusion are associated with inflammation and edema. Diffusion-weighted MRI of the pancreas of T1D individuals detects focal areas of water movement absent in controls without pancreas pathology, possibly reflecting the insulitis associated with T1D.[24] The ability to tune MRI acquisition and processing is both an advantage and disadvantage. Adjusting a number of different acquisition parameters can lead to large differences in imaging protocols across sites. Pancreas imaging needs to be validated against samples with known properties and standardized for comparison across multiple centers.[25] MRI is further limited by cost and necessity to minimize motion artifacts,

typically requiring participants to hold their breath for multiple sequences.

3. Clinical Outlook for Pancreas Imaging in T1D

Pancreas imaging is increasingly providing new information in T1D research. Clinically, pancreatic imaging protocols are unlikely to replace blood-based assays in T1D diagnosis and monitoring due to the ease, speed, and wide adoption of such lab work. However, advanced imaging can provide novel information not captured by blood tests and may be an earlier predictor of T1D progression.[22] Radiologic analysis of the pancreas may also be useful in the development of new therapies by both identifying individuals who may benefit from treatment and assessing response to therapy. Imaging has often been criticized as being too expensive and not widespread enough to reach some patient populations. Recently, given the decline in cost of certain scanners, imaging centers have become more widely distributed. Portable ultrasound and MRI scanners have been developed to further disseminate radiology exams to additional underserved populations. Importantly, imaging of pancreas pathology in T1D need not be a stand-alone test but can be performed at the same time as other abdominal or whole-body scans. Machine learning algorithms are being developed that will screen medical images for a multitude of diseases. Improved understanding of pancreatic disease processes in T1D and development of machine learning techniques to detect pathology will aid integration of pancreas imaging for patients with diabetes into future clinical practice.

Table 1. Comparison of imaging techniques for pancreas imaging in T1D

Imaging Modality	Advantages	Disadvantages
Ultrasound	• Relatively inexpensive • Widespread	• Two-dimensional images • Bowel gas artifact • Operator dependence • Limited functional information
PET	• Further development may enable imaging of endocrine pancreas	• Ionizing radiation • No structural information • Low spatial resolution
CT	• Fast acquisition • High spatial resolution	• Ionizing radiation • Limited functional information • Dependent on type of CT protocol
MRI	• Ability to measure both structural and functional information • Further development may enable imaging both endocrine and exocrine pancreas	• Expensive • Long acquisition times • Motion artifacts from breathing and peristalsis • Variability in sequences and processing techniques

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Contributions:

E.S.H. and J.V. wrote and edited this review. Both authors read and approved the final manuscript.

Conflicts of interest:

The authors declare that they have no competing interests.

Funding:

We gratefully acknowledge support from the National Institutes of Health (HD115565, DK129979), Breakthrough T1D (1-INO-2023-1340-A-N), and the Helmsley Charitable Trust (2201-05374).