Magnetic resonance imaging of pancreatic inflammation in type 1 diabetes

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Background

Areas of inflammation are typically characterized by alterations in vascular parameters, such as vascular volume, flow, and permeability. In models of type 1 diabetes (T1D), modifications of the pancreatic microvasculature accompany the initiation and progression of disease. Vascular swelling and increased blood flow precede insulitis in nonobese diabetic (NOD) mice and in streptozotocin-induced diabetes (1,2). Therefore, the noninvasive monitoring of the pancreatic microvasculature can serve as a valuable diagnostic marker for type 1 diabetes at relatively early stages of the pathology. Previously it has been shown that nontargeted, long-circulating, synthetic polymers can be used for the noninvasive imaging of blood volume changes as well as vascular permeability in animal models of cancer and inflammation (3,4).

In an attempt to detect vascular changes resulting from pancreatic inflammation in type 1 diabetes, we imaged blood volume using MRI enhanced with a long-circulating, biocompatible, and nontoxic paramagnetic T1 contrast agent [PGC; ref (4,5)]. This contrast agent is known to selectively decrease relaxation times of water protons in the vascular compartment without any initial leakage from blood vessels due to a large hydrodynamic diameter corresponding to a globular protein of 1,500 kDa (6).

Methods and Materials

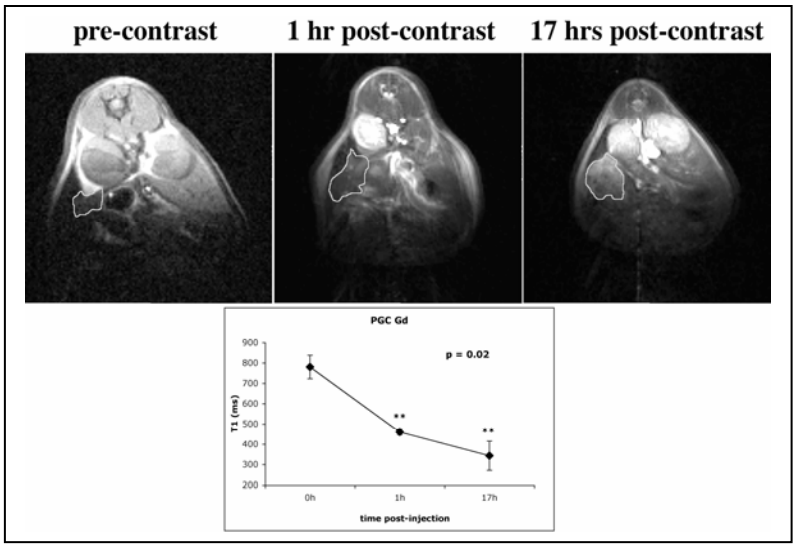
Imaging agent: Protected graft copolymer bearing covalently linked gadolinium-diethylenetriaminepentaacetic acid residues (PGC-Gd) was obtained from PharmaIN, Ltd (Seattle, WA).

Treatment: Balb/c mice were rendered diabetic by i.p. injection of 220mg/kg of the beta-cell toxin streptozotocin (STZ). Diabetic animals were imaged before as well as 1 and 17h after i.v. injection of PGC-Gd (0.4mmol Gd/kg).

Imaging: MR imaging was performed on a 9.4T Bruker horizontal bore scanner (Billerica, MA) equipped with a home-built RF transmit and receive 3 x 4-cm elliptical surface coil and using ParaVision 3.0 Software. T1 maps were acquired using a RARE inversion recovery sequence with the following parameters: TE = 7.253ms, TR = 10,000ms, TI = 0.001, 200, 400, 800, 1600, 3200, and 6400ms. FOV = 25.6 x 25.6mm^2, spatial resolution = 0.2 x 0.2mm.pixel^{-1}, matrix size = 128 x 128, slice thickness = 1mm, and a total imaging time of 16min 5sec. For quantitative analysis of T1 relaxation, T1 color-coded maps were constructed using Marevisi 3.5 software (Institute for Biodiagnostics, National Research Council, Canada). The pancreas was manually segmented and subjected to region-of-interest (ROI) analysis for the determination of pancreas-associated T1 relaxation times.

At the same time points, T1 weighted images of the same mice were obtained using an MSME sequence with the following parameters: TE = 7.841ms, TR = 100ms, FOV = 25.6 x 25.6mm^2, spatial resolution = 0.2 x 0.2mm.pixel^{-1}, matrix size = 128 x 128, slice thickness = 1mm, and a total imaging time of 3min 24sec.

In addition, 3D-angiograms were obtained using a gradient echo imaging sequence comprising first-order flow compensation (GEFC). Image reconstruction was performed using a maximum intensity projection (MIP) algorithm.The following imaging parameters were utilized: TE = 7.16ms, TR = 40ms, FOV = 51.2 x 25.6 x 25.6mm^3, Spatial resolution = 0.4 x 0.4 x 0.4mm.pixel^{-1}, matrix size = 128 x 64 x 64, slice thickness = 25.6mm, and a total imaging time of 2min 46sec.



Results

Our results demonstrated significant accumulation of the long-circulating paramagnetic T1 contrast agent, PGC-Gd in the pancreas of STZ-induced diabetic animals. T1 map analysis revealed a clear increase in the R1 of the pancreas as early as 1h after injection of the probe ($p < 0.05$, Figure). This trend persisted at 17h post-injection. On T1 weighted images, contrast-agent build-up in the area of the pancreas lead to a remarkable signal enhancement as a result of its T1-shorterning effect (Figure). This observation was confirmed using 3-D angiography. These results suggest that the vascular changes accompanying inflammation in type 1 diabetes can be visualized by in vivo MRI, using T1-weighted sequences, following the administration of a strictly vascular contrast agent. Ex vivo validation of our imaging findings as well as an extension of these studies in NOD mice are underway in our laboratory.

Summary

The described imaging approach has both research and therapeutic implications. In models of diabetes, it can deliver new information about the progress of insulitis and the interplay of metabolic and immunological factors in disease initiation and progression. As a potential clinical tool, our method would allow early diagnosis of vascular changes preceding overt diabetes. It would also permit the design of image-guided individualized treatment strategies, based on differences in the degree and timing of inflammation.

References

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