

Noninvasive Magnetic Resonance Imaging of Microvascular Changes in Type 1 Diabetes

Zdravka Medarova,¹ Gerardo Castillo,² Guangping Dai,¹ Elijah Bolotin,² Alexei Bogdanov,³ and Anna Moore¹

OBJECTIVE—The pathogenesis of type 1 diabetes involves autoimmune lymphocytic destruction of insulin-producing β -cells and metabolic dysregulation. An early biomarker of pancreatic islet damage is islet microvascular dysfunction, and alterations in vascular volume, flow, and permeability have been reported in numerous models of type 1 diabetes. Consequently, the ability to noninvasively monitor the dynamics of the pancreatic microvasculature would aid in early diagnosis and permit the assessment, design, and optimization of individualized therapeutic intervention strategies.

RESEARCH DESIGN AND METHODS—Here, we used the long circulating paramagnetic contrast agent, protected graft copolymer (PGC) covalently linked to gadolinium-diethylenetriaminepentaacetic acid residues (GdDTPAs) labeled with fluorescein isothiocyanate (PGC-GdDTPA-F), for the noninvasive semiquantitative evaluation of vascular changes in a streptozotocin (STZ)-induced mouse model of type 1 diabetes. Diabetic animals and nondiabetic controls were monitored by magnetic resonance imaging (MRI) after injection of PGC-GdDTPA-F.

RESULTS—Our findings demonstrated a significantly greater accumulation of PGC-GdDTPA-F in the pancreata of diabetic animals compared with controls. MRI permitted the *in vivo* semiquantitative assessment and direct visualization of the differential distribution of PGC-GdDTPA-F in diabetic and control pancreata. *Ex vivo* histology revealed extensive distribution of PGC-GdDTPA-F within the vascular compartment of the pancreas, as well as considerable leakage of the probe into the islet interstitium. By contrast, in nondiabetic controls, PGC-GdDTPA-F was largely restricted to the pancreatic vasculature at the islet periphery.

CONCLUSIONS—Based on these observations, we conclude that in the STZ model of type 1 diabetes, changes in vascular volume and permeability associated with early stages of the disease can be monitored noninvasively and semiquantitatively by MRI. *Diabetes* 56:2677–2682, 2007

From the ¹Molecular Imaging Laboratory, MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Charlestown, Massachusetts; ²PharmaN, Ltd., Seattle, Washington; and the ³Department of Radiology, University of Massachusetts Medical School, Worcester, Massachusetts.

Address correspondence and reprint requests to Anna Moore, PhD, Molecular Imaging Laboratory, MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Room 2301, Bldg. 149, 13th St., Charlestown, MA 02129. E-mail: amoore@helix.mgh.harvard.edu.

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FITC, fluorescein isothiocyanate; GdDTPA, gadolinium-diethylenetriaminepentaacetic acid residue; MRI, magnetic resonance imaging; PGC, protected graft copolymer; PGC-GdDTPA-F, PGC-GdDTPA labeled with FITC; STZ, streptozotocin.

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The rapid rise in the prevalence of diabetes to ~230 million individuals worldwide during the last 20 years has global implications and requires paradigm-shifting approaches to diagnosis, treatment, monitoring, and prevention. One approach to the early detection of type 1 diabetes would involve the monitoring of changes associated with the pancreatic vasculature. The pancreatic islet is a highly vascularized structure, receiving 10–20% of the blood flow to the pancreas. Typically, islets have one or two afferent arterioles, which give off numerous capillaries to form a glomerular-like network (1). The development of type 1 diabetes is invariably associated with the early onset of local vascular abnormalities. During the course of type 1 diabetes, the endothelial cell layer, which normally represents a barrier to blood leukocytes, allows T-cells to home to, enter, and destroy the islets (2). Changes in vascular permeability in islet blood vessels during the development of type 1 diabetes have been described in both rats (3,4) and mice (5–7). De Papae et al. (3) reported an increase in the permeability of islet capillaries and postcapillary venules at the onset of diabetes in a spontaneous rat model of type 1 diabetes. An increase in islet vascular permeability has also been observed in the diabetes-prone BB rat model (4) and in alloxan-induced murine diabetes (6). Notably, this increase represented the first sign of any morphological abnormality in islet function. In addition, an exciting study in an alloxan-induced rat model showed that fractional islet vascular perfusion reached a remarkable 50% compared with 10% in nondiabetic controls, indicating redirection of pancreatic blood flow through the islets (8). Vascular leakiness has also been observed in the streptozotocin (STZ)-induced diabetes model. A single, high dose of the β -cell toxin, which is the model used in our study, caused a significant increase in islet capillary permeability (5,7,9) detected as early as 1 h after STZ administration (9). Importantly, increased islet microvascular permeability was seen before the animals became diabetic and before signs of pancreatic insulinitis (5). These studies suggest a strong link between the increase in vascular flow and permeability and type 1 diabetes. Furthermore, it appears that changes in the islet microvasculature precede other symptoms of the disease, such as advanced inflammation, hyperglycemia, and morphological abnormalities. Consequently, the local microvasculature represents an excellent diagnostic biomarker for the earliest stages of islet dysfunction. However, despite the important role of the microvasculature in the pathogenesis of type 1 diabetes, the extent and time course of pancreatic microvascular changes are still unknown.

All of the above-cited studies on islet vasculature are generally limited to histological postmortem findings,

which suffer from the need for tissue processing and the inability to study the dynamics of blood flow. In this context, noninvasive imaging seems to be the most appropriate approach to studying the dynamics of the islet vasculature *in vivo*. Previous studies using superparamagnetic iron oxides for monitoring the blood pool in a model of diabetes did not permit the direct visualization of the vasculature through angiography due to the negative nature of the T2 contrast agent used in this study (10,11). Here, we describe a novel approach for the characterization of pancreatic vascular changes in a model of type 1 diabetes using high-resolution *in vivo* magnetic resonance imaging (MRI) in combination with a novel nanocarrier delivery system. We used a nano-sized protected graft copolymer (PGC) (12) covalently linked to gadolinium-diethylenetriaminepentaacetic acid (GdDTPA) residues labeled with fluorescein isothiocyanate (FITC) (PGC-GdDTPA-F) as a blood pool imaging agent for the delivery of a T1-positive paramagnetic contrast agent (GdDTPA) to image the vascular compartment. PGC-GdDTPA has a large hydrodynamic diameter corresponding to a globular protein of 1,500 kDa and carries protective groups of polyethylene glycol for minimal uptake by the reticuloendothelial system. It selectively distributes within the vascular bed without any initial leakage from blood vessels and can be used to enhance both the arterial and venous vascular compartments with submillimeter resolution (13,14). The application of PGC-GdDTPA as a blood pool agent has been studied in detail in models of tumor vascular dysfunction (13,15–17) and angiogenesis (14).

In the presence of inflammation, PGC-GdDTPA accumulates extensively in areas of high capillary permeability and increased blood flow, including outside the vascular compartment, due to leakage across the hyperpermeable vascular endothelium (12). This effect and its application in the context of MRI and nuclear imaging have been applied in a model of soft tissue bacterial infection (18).

Here, we describe the application of PGC-GdDTPA in a model of type 1 diabetes. This is the first report of noninvasive blood volume imaging for the semiquantitative *in vivo* definition of pancreatic microvasculature dynamics in type 1 diabetes. We believe that this study provides valuable information on islet vasculature during diabetes progression, which could serve not only as a scientific research tool but also as a practical way to stage and monitor islet inflammation and vascular dysfunction in a future clinical scenario.

RESEARCH DESIGN AND METHODS

Imaging agent. PGC-GdDTPA-F was obtained from PharmaIN (Seattle, WA). **Animals and treatment.** Five-week-old female BALB/c mice ($n = 6$, ~20 g) were rendered diabetic by injection of 200 mg/kg *i.p.* of the β -cell toxin STZ. On the following day, diabetic animals were imaged before as well as 1, 17, and 40 h after intravenous injection of PGC-GdDTPA-F (0.2 mmol gadolinium/kg). Age-matched nondiabetic animals injected with PGC-GdDTPA-F and imaged at the same time points served as controls ($n = 4$).

Fasting blood glucose levels were determined 24 h after STZ administration using Glucometer Elite Testing System (Bayer Diagnostics, Tarrytown, NY). All animal experiments were performed in compliance with institutional guidelines approved by the Subcommittee on Research Animal Care at the Massachusetts General Hospital and in accordance with the National Institutes of Health Principles of Laboratory Animal Care (publ. no. 85-23, revised 1985).

In vivo MRI. MRI was performed on a 9.4T Bruker horizontal bore scanner (Billerica, MA) equipped with a home-built radio frequency transmit and receive 3×4 cm elliptical surface coil and using ParaVision 3.0 software. For *in vivo* imaging of diabetic and control mice, we obtained T1 maps, T1-weighted images, and low- and high-resolution 3D angiograms. Details on

image sequences and image analysis can be found in the online appendix (available at <http://dx.doi.org/10.2337/db07-0822>).

PGC-GdDTPA-F localization in the pancreas by histology. PGC-GdDTPA-F was synthesized to carry a fluorescent label (FITC). Fluorescence microscopy on pancreata from experimental and control animals was performed in two channels (FITC for PGC-GdDTPA-F and DAPI for nucleus). Consecutive sections were stained with hematoxylin and eosin and analyzed by light microscopy. Additional tissue sections were stained for insulin and analyzed by fluorescence microscopy. Details on the staining procedures are presented in the online appendix.

RESULTS

To evaluate microvascular changes in the diabetic pancreas, we used the long-circulating paramagnetic T1 contrast agent, PGC covalently linked to GdDTPA labeled with fluorescein. PGC-GdDTPA-F was administered to STZ-induced diabetic mice (fasting blood glucose 287.8 ± 186.9 mg/dl [range 24–450]) and nondiabetic controls (114.0 ± 22.1 mg/dl [range 94–141]). Our results demonstrated sufficient accumulation of the agent in the pancreas for detection by MRI. On T1-weighted images obtained 17 h after injection of the contrast agent into STZ-induced diabetic animals, the pancreas was clearly enhanced compared with preinjection images due to the T1-shortening effect of GdDTPA (Fig. 1A).

Quantitative time-course analysis of T1 relaxation times was based on inversion-recovery T1 maps (Fig. 1B). These studies indicated accumulation of PGC-GdDTPA-F in the pancreata of both diabetic animals and nondiabetic controls, as early as 1 h postinjection, reflective of presence of the contrast agent in the blood pool. The peak of contrast agent bioavailability in the pancreas was reached 17 h after injection, followed by a gradual washout by 40 h (Fig. 1C). While we observed the expected vascular enhancement in both animal groups, the levels of PGC-GdDTPA-F in the pancreata of diabetic animals were significantly higher than in those of nondiabetic control animals ($P < 0.05$), consistent with increased blood volume and vascular permeability. This difference was reflected by a lower T1 in diabetic mice compared with controls and was seen at 1 h (diabetic T1 385.9 ± 30.1 ms and nondiabetic T1 501.3 ± 43.3 ms) and 17 h (diabetic T1 193.7 ± 3.5 ms and nondiabetic T1 342.5 ± 52.8 ms) after injection of PGC-GdDTPA-F (Fig. 1C).

To monitor the whole-body vascular distribution of PGC-GdDTPA-F, we performed low-resolution 3D angiography of the same animals at the specified time points. As seen in Fig. 2, using a $0.4 \times 0.4 \times 0.4$ mm/pixel resolution, we could see significant enhancement in the upper left abdomen, consistent with the location of the pancreas, in diabetic animals but not in nondiabetic controls. The time course of this enhancement closely matched our T1 map analysis. It became apparent at 1 h postinjection of PGC-GdDTPA-F, increased at 17 h, and became negligible by 40 h after contrast agent delivery (Fig. 2).

For more precise identification of the origin of this signal, we imaged diabetic mice and controls using high-resolution 3D angiography. Brightly enhancing arteries and less-enhancing veins labeled with fluorescein could be distinguished at the $0.1 \times 0.1 \times 0.1$ mm/pixel resolution. The hepatic vasculature was clearly identifiable in both experimental and control animals, as a result of contrast agent availability in the blood pool. Notably, we observed a clear and remarkable enhancement in the area of the pancreas in diabetic animals due to the vascular leakage of the agent as early as 1 h after injection, followed by a washout from the pancreas by 40 h (Fig. 3 and online

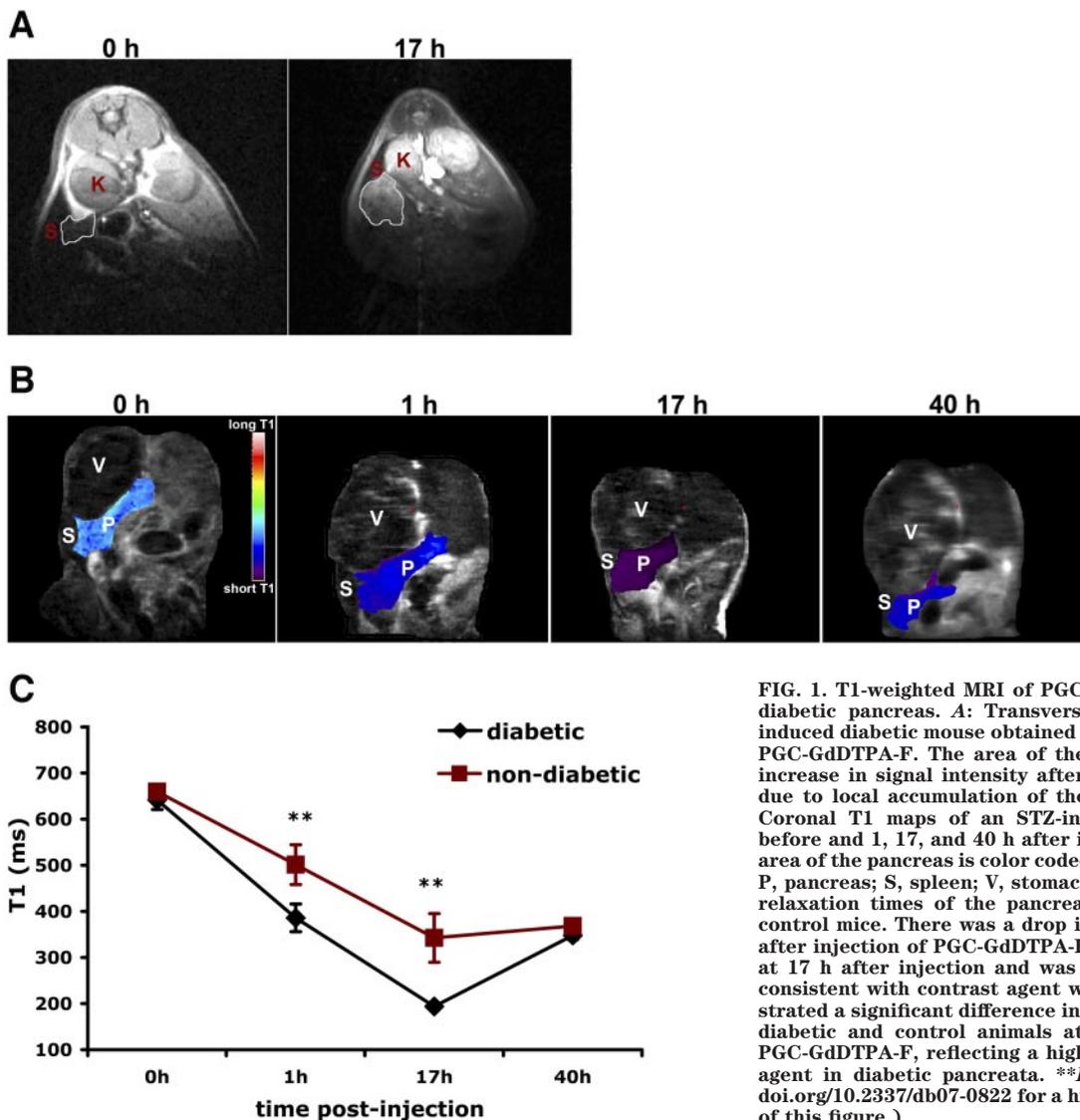


FIG. 1. T1-weighted MRI of PGC-GdDTPA-F accumulation in the diabetic pancreas. **A:** Transverse T1-weighted MRI of an STZ-induced diabetic mouse obtained before and 17 h after injection of PGC-GdDTPA-F. The area of the pancreas is outlined. Note the increase in signal intensity after injection of the contrast agent due to local accumulation of the agent. K, kidney; S, spleen. **B:** Coronal T1 maps of an STZ-induced diabetic mouse obtained before and 1, 17, and 40 h after injection of PGC-GdDTPA-F. The area of the pancreas is color coded based on its T1 relaxation time. P, pancreas; S, spleen; V, stomach. **C:** Quantitative analysis of T1 relaxation times of the pancreata of STZ-induced diabetic and control mice. There was a drop in the T1 of the pancreata at 1 h after injection of PGC-GdDTPA-F. This drop was most significant at 17 h after injection and was followed by a gradual increase, consistent with contrast agent washout. T1 map analysis demonstrated a significant difference in the T1 of the pancreata between diabetic and control animals at 1 and 17 h after injection of PGC-GdDTPA-F, reflecting a higher accumulation of the contrast agent in diabetic pancreata. ** $P < 0.05$. (Please see <http://dx.doi.org/10.2337/db07-0822> for a high-quality digital representation of this figure.)

appendix supplemental movies 1 and 2). No such enhancement in the pancreas was observed in control animals. As expected based on the long circulation half-life of PGC-GdDTPA-F (14 h in rodents [12]), residual levels of contrast agent in the larger hepatic arteries caused the enhancement of these vessels to persist even at the 40-h time point.

Finally, to independently validate our findings, we correlated our imaging conclusions with gold standard histological measurements of the tissue distribution of the contrast agent. On hematoxylin and eosin sections, we could identify pancreatic islets adjacent to islet-feeding pancreatic blood vessels (Fig. 4A). In STZ-induced diabetic mice, however, pancreatic islets were less abundant and islet morphology appeared abnormal (Fig. 4A). The detrimental effect of STZ on islet architecture was further confirmed by staining for insulin (online appendix supplemental Fig. 1). Fluorescence microscopy demonstrated a significant accumulation of PGC-GdDTPA-F in the pancreata of diabetic animals. There was bright green fluorescence, associated with the presence of PGC-GdDTPA-F, in blood vessels feeding pancreatic islets. Fluorescence intensity was markedly enhanced in experimental versus control animals, consistent with increased vascular volume (Fig. 4B and supplemental Fig. 2). Diffuse green

fluorescence associated with the islet interstitium and present exclusively in tissue sections from diabetic but not control animals was consistent with extravascular leakage of the contrast agent. In control animals, fluorescence derived from PGC-GdDTPA-F was restricted to the islet periphery (Fig. 4C).

DISCUSSION

Accumulating evidence suggests that the vascular endothelium is of crucial importance for the development of inflammatory responses in the pancreas. In models of type 1 diabetes, modifications of the pancreatic microvasculature accompany the initiation and progression of disease. Vascular swelling and increased blood flow precede insulinitis in nonobese diabetic mice and in STZ-induced diabetes (5,7,9,19,20). Consequently, pancreatic islet vascular dysfunction is a crucial element of the pathology of type 1 diabetes and therefore represents an early and potentially predictive biomarker for the loss of β -cell mass. In addition, vascular changes have also been reported in type 2 diabetes. Augmented islet blood flow has been demonstrated after short-term modest hyperglycemia, as well as in several animal models of type 2 diabetes, including the

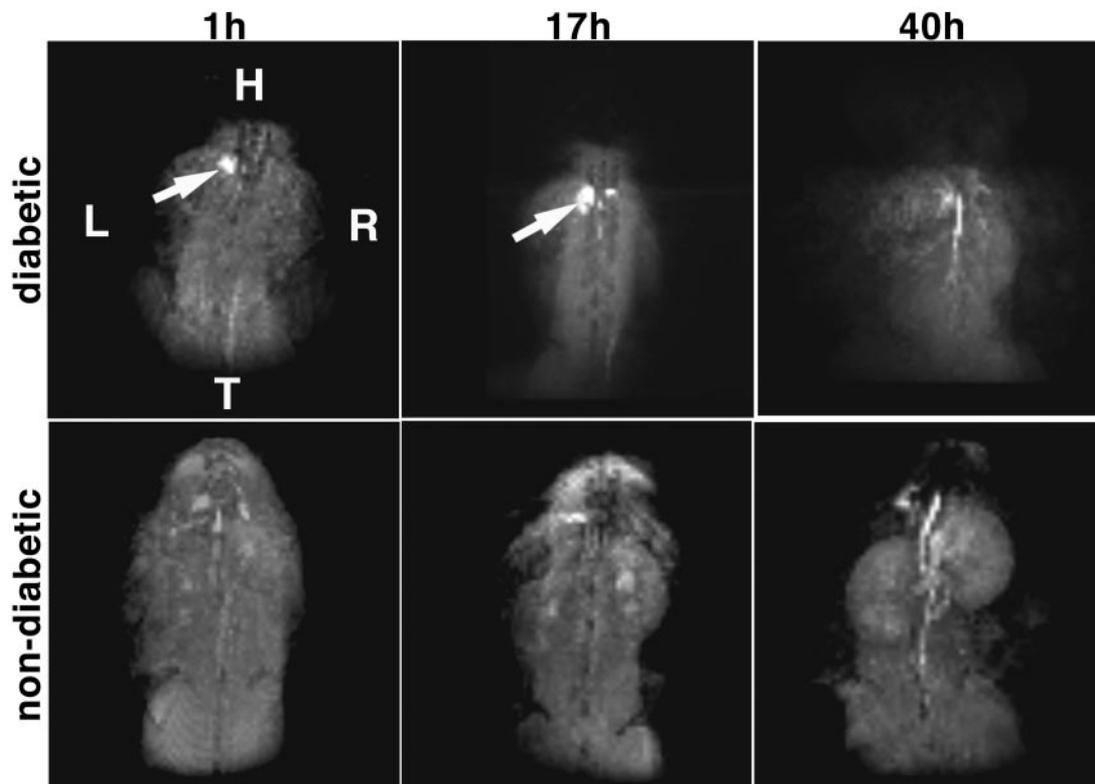


FIG. 2. Low-resolution 3D MR angiography of STZ-induced diabetic mice and nondiabetic controls obtained 1, 17, and 40 h after injection of PGC-GdDTPA-F. The pancreas is enhanced in diabetic animals at 1 h postinjection (arrows), followed by a washout by 40 h. No clear enhancement of the pancreas is seen in nondiabetic controls. H, head; L, left; R, right; T, tail.

Goto-Kakizaki (GK) rat (21) and the obese hyperglycemic mouse (22).

Overall, pancreatic vascular dysfunction seems to play a

critical role in both type 1 and type 2 diabetes and represents a complex multifactorial system that cannot be studied without a comprehensive systematic approach. In vivo MRI has been widely used to characterize vascular events in the brain and in various types of tumors (23–25). Here, we apply this methodology to study the islet vasculature. To the best of our knowledge, this represents the first application of magnetic resonance angiography to visualize islet vascular dysfunction using a paramagnetic blood pool imaging agent. Differential accumulation of PGC-GdDTPA-F in the pancreatic area detected by this technique was clearly identifiable in STZ-induced diabetic animals but not in healthy controls. In our experiments, we used the exaggerated single-high-dose STZ model of diabetes because it provides a solid framework for the establishment of proof-of-principle for our imaging method. The next logical step in our studies, however, is to test the feasibility of this approach in the multiple-low-dose STZ model, nonobese diabetic mice, as well as in models of type 2 diabetes. These models more closely resemble human pathology and therefore such studies would help assess the sensitivity of this method and its feasibility in a potential future clinical scenario. Furthermore, because the observed effects are the result of two separate events (increased vascular volume and permeability), further studies would be necessary to unravel the relative input of each. We believe that this imaging strategy represents a valuable research tool for studying 1) the time course of the disease, 2) the role of the vasculature in the insulinitic process and islet cell death relevant to type 1 diabetes, and 3) the vascular response to metabolic dysregulation in both type 1 and type 2 diabetes. In a therapeutic scenario, the described methodology has im-

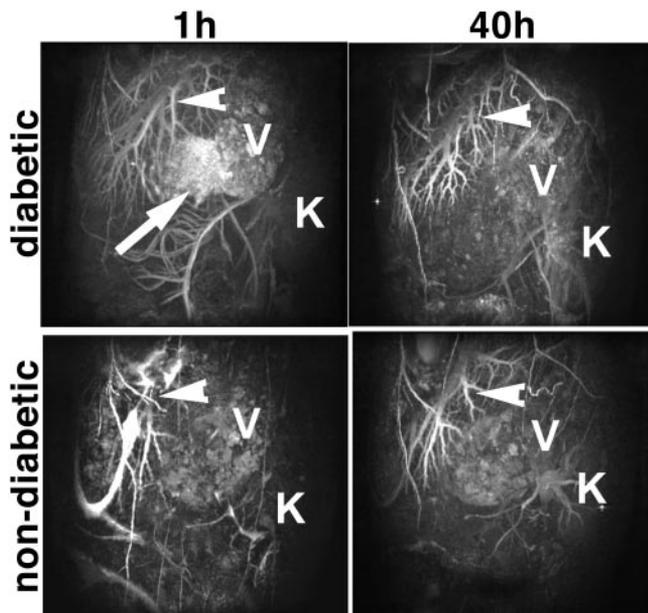


FIG. 3. High-resolution 3D MR angiography of STZ-induced diabetic mice and nondiabetic controls obtained 1 and 40 h after injection of PGC-GdDTPA-F. The hepatic vasculature is outlined following injection of the contrast agent (arrowheads). In diabetic animals, the pancreas is associated with bright diffuse enhancement at 1 h postinjection (arrow), consistent with increased vascular volume and leakage into the interstitium. This is followed by a washout by 40 h. Nondiabetic animals showed no enhancement in the area of the pancreas. K, kidney; V, stomach.

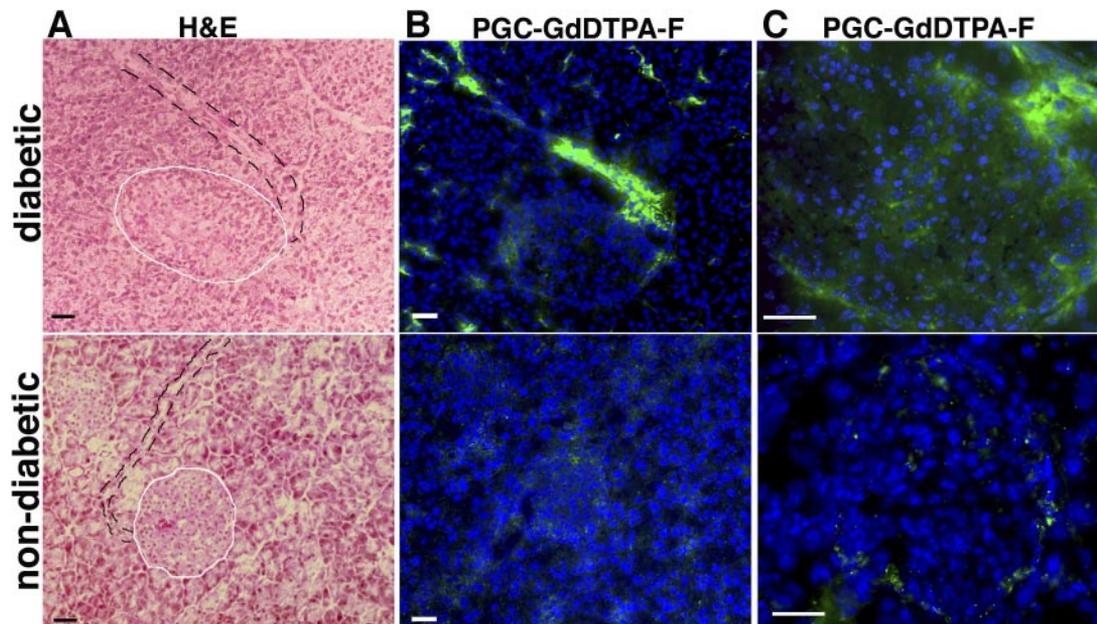


FIG. 4. Histology of pancreata derived from STZ-induced diabetic and nondiabetic control mice. **A:** Pancreatic islets adjacent to blood vessels could be identified in hematoxylin and eosin sections. **B:** Bright green fluorescence could be seen in islet-feeding blood vessels. Fluorescence intensity was markedly higher in diabetic than control animals, suggesting greater vascular volume in diabetic mice. **C:** Diffuse green fluorescence associated with the islet interstitium was seen in diabetic but not control mice indicating extravascular leakage of PGC-GdDTPA-F. By contrast, in nondiabetic controls, green fluorescence was restricted to the islet periphery. **A and B:** Original magnification bar, 50 μm . **C:** Original magnification bar 20 μm . (Please see <http://dx.doi.org/10.2337/db07-0822> for a high-quality digital representation of this figure.)

plications for the early diagnosis of diabetes, the monitoring of events relevant to islet transplantation and other diabetes therapies, and the design of image-guided individualized treatment strategies.

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