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Persistent cerebrovascular damage after stroke in type two diabetic rats measured by MRI

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Abstract

Background and purpose—Diabetes is a disease with vascular components. Consequently, the BBB disruption post stroke may differ between diabetic and non-diabetic animals. However, few studies have documented the longitudinal BBB disruption post stroke in diabetic animals. In this study, using MRI, we non-invasively evaluated the BBB damage after MCAo in diabetic and non-diabetic rats.

Methods—T2DM was induced in adult male Wistar rats by administration of a high fat diet in combination with a single intraperitoneal injection (35mg/kg) of Streptozotocin. T2DM rats (n=9) and non-diabetic wild-type (WT) rats (n=9) were subjected to MCAo for 2h using the filament model. MRI was performed one day and then weekly for 5 weeks post MCAo for all rats.

Results—The ischemic lesion volumes post stroke as measured using T2 maps were not significantly different between the T2DM and WT rats. Compared to the WT rats, the volumes of BBB disruption evaluated using CE-T1WI with Gd-DTPA, and the cerebral hemorrhagic volumes measured with SWI were significantly ($p<0.05$) larger in the T2DM rats from 1w to 5w after stroke; values of diffusion fractional anisotropy (FA) were significant lower in T2DM rats ($p<0.03$) than in WT rats after stroke. These MRI measurements were consistent with histological data.

Conclusions—Using MRI, T2WI did not detect significant differences of the ischemic lesion volumes between T2DM and WT rats. In contrast to the WT rats, however, CE-T1WI and SWI identified much more severe ischemic vascular damage, while FA demonstrated lower axonal density in the T2DM rats after stroke.

Keywords

Diabetes; MRI; Stroke; BBB; Hemorrhage; Rat

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Conflict of interest disclosures

No conflicts are declared for all authors. The content is solely the responsibility of the authors and does not necessary represent the official view of the National Institute of Health.

Introduction

Diabetes mellitus is a chronic vascular disease.[1] Hyperglycemia induces a variety of biochemical changes within endothelial cells, including those in the cerebral vasculature.[2] Diabetes instigates a cascade of events leading to vascular endothelial cell dysfunction, and increased vascular permeability in various vascular beds in humans and animal models.[3] Many pathways are involved in the diabetes-related changes in the blood-brain barrier (BBB).[4,5] In the clinic, the vast majority (90–95%) of diabetic patients have type 2 diabetes mellitus (T2DM), which affects 24 million Americans.[1]

Diabetes increases risk of ischemic stroke more than hemorrhagic stroke.[6] Clinical and experimental results have demonstrated that diabetes also increases stroke recurrence and long-term mortality from stroke, and worsens the overall neurological outcomes after stroke.[6–8] Abnormalities in glucose metabolism and vascular hemodynamics may play important roles in the pathogenic progress of stroke in diabetic patients.[6]

Experimental studies have reported inconsistent ischemic lesion volumes in diabetic rodents compared to non-diabetic rodents, which may depend on the type and duration of diabetes, ischemia model, or the murine strain.[8,9] Here, we employed magnetic resonance imaging (MRI) to longitudinally measure the ischemic lesion volumes using a filament model of stroke in adult rats with or without T2DM diabetes induced by Streptozotocin combined with a high fat diet.[10,11]

BBB damage and exacerbated secondary hemorrhagic transformation (HT) are consistent consequences of ischemic stroke in diabetic murine animals.[9,12] However, prior preclinical studies only focused on the measurement of BBB disruption and cerebral vascular permeability rate at an early stage after stroke in diabetic animals using histological methods, which do not allow dynamic evaluation and application to patients. In the present study, by employing MRI, the temporal characteristics of BBB disruption were monitored weekly up to 5 weeks after stroke in the T2DM and non-diabetic wild-type (WT) rats. These results may provide new information on dynamic and chronic cerebrovascular damages after stroke in T2DM rats.

Materials and Methods

All experimental procedures were conducted and performed in accordance with guidelines for animal research under a protocol approved by the Institutional Animal Care and Use Committee of Henry Ford Hospital.

Animal model and experimental protocol

T2DM was induced[10,11] in adult (175g, 2~3M) male Wistar rats (Charles River, Wilmington, MA) by feeding them a high fat diet (HFD, 40% of calories as fat) for 2 weeks, then injecting a single intraperitoneal (i.p.) dose, 35mg/kg, of Streptozotocin (Zanosar®, Sigma Chemical Co., St. Louis, MO), a naturally occurring chemical that is particularly toxic to the insulin-producing beta cells of the pancreas in mammals, the HFD was

continued for another two weeks. Blood glucose level was measured using test strips for glucose (Polymer Technology System, Indianapolis, IN) for confirmation of hyperglycemia (449.2±42.6mg/dL and 414.2±134.6mg/dL at 1d before and after MCAo). Right middle cerebral artery occlusion (MCAo) was then induced for 2 hours using the filament model, as previously described.[13] Briefly, a 4-0 monofilament nylon suture, its tip rounded by heating, was introduced into the internal carotid artery lumen through the stump of the external carotid artery and gently advanced into the internal carotid artery 19–21mm past the common carotid artery bifurcation to block the origin of the middle cerebral artery. Reperfusion was initiated through removal of the thread and tying off the distal external carotid artery. Wistar rats, fed normal chow (12% of calories as fat) without Streptozotocin injection, received suture induced ischemia-reperfusion injury, and were used as the WT control rats (blood glucose level: 93.3±2.1mg/dL and 90.8±5.6mg/dL at 1d before and after MCAo). The control and T2DM animal groups were age matched.

MRI was performed prior to the surgery for MCAo, as an internal control. Then, MRI was performed at one day and then weekly for 5 weeks after ischemia-reperfusion for all rats. Three T2DM rats and one WT rat died after MCAo and were excluded from the study. After completing MRI scans, all animals (n=9 for T2DM and n=9 for WT rats) were euthanized 5 weeks post stroke.

MRI measurements

MRI measurements were performed with ClinScan 7T system, which combines Bruker-Biospin hardware (Bruker-Biospin, Ettlingen, Germany) with Siemens software (Siemens, Erlanger, Germany). A birdcage type coil was used as the transmitter and a quardrature half-volume coil as the receiver. Pulse sequences included T2-weighted imaging (T2WI), susceptibility weighted imaging (SWI), diffusion weighted imaging (DWI) with multiple directions and contrast enhanced T1-weighted imaging (CE-T1WI) with Gd-DTPA, gadolinium-diethylenetriamine penta-acetic acid (Magnevist®, Berlex Inc, Montville, NJ), as the image contrast agent.

A fast gradient echo imaging sequence was used for reproducible positioning of the animal in the magnet at each MRI session. During MRI measurements, anesthesia was maintained using medical air (1.0L/min) with isoflurane (1.0–1.5%). Stereotactic ear bars were used to minimize movement, and rectal temperature was maintained at 37±1.0°C using a feedback controlled water bath (YSI Inc, Yellow Springs, OH).

T2WI was acquired using a multislice (13 slices) and multiecho (6 echoes) sequence, with time of echo (TE) as 15ms, and equally to 90ms. The time of repetition (TR) was 4.5sec. Images were produced using a 32×32mm^2 field-of-view (FOV), 1mm slice thickness, 128×64 matrix. SWI employed a specialized 3-dimensional gradient echo sequence with TE=10ms, TR=40ms, flip angle of 15°, 32×32×24mm^3 FOV, 256×192×64 matrix, and flow compensation in all three directions. DWI was acquired using a spin-echo sequence with pulsed diffusion weighted gradients and one-shot echo-planar readout. The FOV was 32×32mm^2; 128×128 matrix, 1mm slice thickness with 13 slices, TR=10s and TE=50ms, one baseline of b=0s/mm^2, 128 directions of diffusion gradients with b=1500s/mm^2 for each slice. CE-T1WI was composed of two T1WI acquisitions, before and 6 minutes after

injection of Gd-DTPA into a tail vein at a dose of 0.4mL/kg. T1WI was acquired using a conventional multislice single spin-echo sequence with TE of 8ms and TR of 500ms. The other MRI parameters in T1WI were the same as in T2WI.

Histological staining

Rats were euthanized with ketamine (44mg/kg i.p.) and xylazine (13mg/kg i.p.). Brains were isolated, post-fixed in 4% paraformaldehyde for 2 days at room temperature, and then processed for paraffin sectioning. Coronal sections (6μm thick) were cut from each block and stained with hematoxylin and eosin (H&E) for the evaluation of ischemic lesion and blood in cerebral parenchymal tissue using light microscopy. Perls Prussian Blue (PPB) stain was performed for measurement of iron in cerebral parenchymal tissue, as evidence of hemorrhage. Double Bielschowsky's silver and Luxol fast blue (BLFB) staining was performed for evaluation of axon and myelin.

Data and statistical analysis

Data analysis was performed in a blind fashion. MRI image analysis was generally performed with homemade software, Eigentool.[14] T2 maps were obtained pixel-by-pixel by using a linear least-squares fit to the plot of the natural logarithm. SWI was analyzed using SPIN software.[15] The multi-direction DWI analysis was performed using Camino software.[16] FA map was derived from the multi-direction DWI.

Ischemic lesion volumes of MRI were measured on the T2 maps. The mean plus two times standard deviation (SD) of the contralateral measurements on the T2 maps was used as a threshold to identify lesion volume. To eliminate the influence of brain atrophy after stroke, the ischemic lesion volume were calculated and expressed as the ratio of lesion volume to contralateral hemispheric volume. The same measurement was performed on the subtraction image of pre-Gd T1WI from post-Gd T1WI.[17] Due to hypointensity of hemorrhage on the SWI intensity image, the mean minus two times SD of the contralateral measurements was used as threshold to identify HT after stroke.[14] T1WI and SWI measurements were presented as the direct volumes. FA measurement was performed with one slice matched the histological section C for each animal. The difference of ischemic lesion areas obtained from the same slice of T2 map between 1d and 5w after stroke was referred as the, recovery region-of-interest (ROI). The FA map was first warped to the corresponding T2 map; then, the ROIs within the striatum were loaded onto the FA map for measurement.

The MicroComputer Imaging Device (MCID) system (Imaging Research Inc, Ontario, Canada) was used for histological measurements. H&E and PPB stained sections were evaluated at 20×, or 40× magnifications, respectively. With BLFB staining, four locations of the coronal section were used for axonal density quantification.[7] The reactive areas of the recovery ROI inside striatum were measured (percentage to FOV) under a 40× objective of optical microscope, using an average of all locations as the histological result.

Analysis of variance was performed. The effect was detected at the 0.05 level. Student's *t*-test was applied between animal groups of MRI measurements obtained at the same time points. MRI measurements are summarized as mean and SD.

Results

The ischemic lesion volumes quantitatively measured by T2 maps, indicated in Figure 1A, do not exhibit any significant differences ($p>0.05$) during the period of 1d to 5w after stroke between the T2DM (33.8%±15.3% at 5w) and WT (28.7%±16.3% at 5w) rats. Representative MRI T2 maps from 1 day to 5 weeks after stroke are shown in Figure 2 for T2DM and WT rats. With the edema declining with time post stroke, the volume of the ischemic lesion consequently experienced large changes from 1d to 1w after stroke for all rats (Fig. 1A). Small changes of the ischemic volume were detected starting at 1 week after stroke for both T2DM and WT animals (Fig. 1A). Lesion volumes from T2 maps exhibited similar temporal profiles for both T2DM and WT rats (Fig. 1A). The infarction volumes measured from the histological H&E coronal sections using the MCID system were 37.9±10.4 percent of the contralateral hemisphere for the T2DM rats, and 27.8±5.9 percent for the WT rats. However, no significant differences were detected between the T2DM and WT rats at 5w after stroke ($p>0.05$).

Unlike the lesion volumes, BBB disruption volumes of the T2DM rats measured with CE-T1WI of Gd-DTPA exhibited significant differences from the WT rats, as quantitatively demonstrated in Fig. 1B. The volumes with Gd-DTPA enhancement acquired with CE-T1WI were significantly ($p<0.05$) larger in the T2DM rats than in the WT rats from 1w to 5w after stroke, which indicates that BBB disruption was significantly worse in T2DM rats up to 5 weeks after stroke, compared to the WT rats.

Figure 3 presents subtracted images of pre-contrast from post-contrast T1WI for two representative animals. The areas with hyperintensity in the images, which indicated the leakage of Gd-DTPA through BBB, persisted from 1 to 5 weeks post stroke in the T2DM rat. However, for the WT rat, subtracted T1WI images presented hyperintensity areas only at 1 day post stroke (arrow in Fig. 3), which suggested that the BBB leakage of Gd-DTPA was present only on the first day post stroke. No evident Gd-DTPA leakage was found after that in the WT rat.

BBB disruption after ischemia may lead to HT. The hypointensity areas excluding veins in the SWI images are associated with hemorrhage.[18] Quantitative SWI measurements of hemorrhagic volumes, as shown in Fig. 1C, demonstrated that the T2DM rats exhibited significantly ($p<0.005$) larger hemorrhagic volumes (approximately 10 times) than WT rats from 1w to 5w after stroke. The representative T2DM and WT rats exhibited different evolutions of the HT after ischemia with SWI images in Figure 4. From the SWI images, areas of hypointensity which reflect hemorrhage, indicated by arrow heads in Fig. 4, actively changed morphologically during 1d to 5w after stroke in the T2DM rat. While hemorrhage spots identified in the WT rat changed little; where hemorrhage was detected starting at 1w and no apparent change was subsequently found to 5w after stroke. The hypointensity areas are much larger in the T2DM rat than in the WT rat.

Erythrocytes outside of blood vessels in the cerebral parenchymal tissue indicate hemorrhage. Analysis of H&E histological coronal sections under the light microscope showed that the red cells were diffusively present in the ischemic cerebral tissue in the

T2DM rat, shown in Fig. 5A; while the red blood cells were localized in a smaller region in the WT rat (Fig. 5B). PPB stains were consistent with H&E stains. The Prussian blue spots outside of blood vessels in the brain parenchymal tissue were larger in size and much darker in color for the T2DM rat (Fig. 5C) than that for the WT rat (Fig. 5D). Combining the histological results of H&E and PPB staining for short- and long-term hemorrhage, respectively, the T2DM rat evidently had more severe and extensive hemorrhage after stroke than the WT rat, which coincided with the MRI measurements.

The temporal profiles of FA values of the recovery striatal tissue are demonstrated in Fig. 1D. The FA values remained significantly ($p<0.02$) lower within 5w after stroke for T2DM rats, compared to the WT group. The mean values of FA were 0.31±0.08 for the WT group and 0.20±0.05 for the T2DM group at 5 weeks after stroke. The axonal densities were histologically measured at 5w after stroke on BLFB staining sections, as 24.1±7.7 percent for the WT group versus 17.4±5.3 percent for the T2DM group, which is significantly different ($p<0.05$) and consistent with FA measurements. However, the functional outcomes of mNSS[8] were marginally different ($p<0.06$) between the control (5.89±0.60) and T2DM (6.89±1.27) groups at 5w after MCAo.

Discussion

Clinical data indicate that non-diabetic patients with transient hyperglycemia have smaller infarction volumes after stroke than diabetic patients.[19] Preclinical results on infarction size in diabetic and non-diabetic animals are equivocal. Preexisting hyperglycemia significantly exacerbates the ischemic lesion volumes in most brain regions at 4h after stroke in adult Sprague-Dawley rats with a 2h/2h suture ischemia-reperfusion injury compared with normoglycemic cohorts.[20] However, compared with normoglycemia, the infarct volume was decreased in hypoglycemic rats, and unaltered in acute diabetes induced by single Streptozotocin injection 2 days before MCAo. With the T2DM model in Goto-Kakizaki rats, infarction volumes were significantly smaller and independent of the 3h/21h of ischemia-reperfusion filament,[9] or 24h embolic MCAo models.[3] Conversely, infarction volumes were significantly increased after stroke in T2DM mice compared to non-diabetic mice.[7,12] Thus, there is a need to delineate the ischemic lesion volume for our animal model, a T2DM model induced by a single intraperitoneal injection of low dose Streptozotocin combined with a HFD, and a 2h suture ischemia-reperfusion model in the young adult Wistar rat. By employing dynamic T2WI measurements in the current study, shown in Fig. 1A, the cerebral infarction volume of T2DM rats was not significantly different from that of non-diabetic controls from 1d to 5w after stroke. Histological measurements of infarction at 5w after stroke present consistent results with MRI. This preclinical result, interestingly, coincides with the clinical outcome.[21]

Unlike neuronal damage after stroke, more severe vascular damage has been consistently documented in stroke patients and animals with diabetes.[3,4] However, in previous preclinical reports, BBB disruption and permeability rate in diabetic animals were regionally measured shortly after stroke from stained cerebral tissue sections, and measurements were limited to a one time measurement by using histological methods.[3,7,12] In contrast, by employing MRI in the present study, longitudinal measurements of BBB disruption were performed in stroke

rats with or without T2DM from 1 day to 5 weeks post ischemia-reperfusion stroke. At 24h after stroke, T2DM rats had a marginally larger BBB disruption volume ($p<0.08$) than WT rats. The MRI data, as shown in Fig. 1B, demonstrated that T2DM rats exhibited significantly larger volumes of BBB disruption, as indicated by measurement of Gd-DTPA leakage, starting from 1 week and persisted to 5 weeks after stroke ($p<0.005$), compared with WT rats. These data indicate that BBB disruption after stroke is a long-term problem in T2DM rats, which persists for at least 5 weeks after stroke. Vascular remodeling prior to MCAo in the T2DM rats due to hyperglycemia was not separately investigated in this study.

BBB disruption may lead to HT after ischemia. When blood cells leave a ruptured blood vessel, the erythrocytes die, and the hemoglobin of the cell is released into the extracellular space. With the hemoglobin losing oxygen, diamagnetic oxyhemoglobin becomes paramagnetic deoxyhemoglobin. Phagocytic cells engulf the hemoglobin to degrade it, producing hemosiderin, an iron-storage form, always found within cells (as opposed to circulating in blood). Thus, hemosiderin is most commonly found in macrophages and is especially abundant in situations following hemorrhage, which can be identified histologically by Prussian blue stain, and importantly, by SWI.[22]

Since deoxyhemoglobin and hemosiderin present after hemorrhage, SWI is employed to detect the hemorrhagic transformation after ischemia. As shown in Fig. 1C, hemorrhagic volumes identified by SWI were significantly larger in T2DM rats than in WT rats from 1d to 5w after stroke ($p<0.05$). Histological H&E and PPB staining pictures (Fig. 5) support SWI results, which show increased hemoglobin (Fig. 5A) for new hemorrhage and hemosiderin (Fig. 5C) for old hemorrhage in the T2DM rat compared with the WT rat (Fig. 5B & D), respectively.

MRI FA was able to monitor well-reorganized white matter, and FA has been employed as an index of white matter recovery after treatment of stroke in rats.[23] In the present study, the temporal profiles of FA measurements (Fig. 1D) demonstrated a significant decrease ($p<0.02$) in FA of the white matter in the recovery ROI extending from the corpus callosum to the boundary of the stroke lesion in the T2DM rats, in contrast to the WT controls. These data suggest that T2DM may hamper the white matter reorganization involving the corpus callosum after stroke. The histological measurements with BLFB stained sections parallel results as the MRI FA, that is, axonal density along the ischemic boundary in striatum was significantly lower ($p<0.05$) in the T2DM rats than in WT rats at 5w after stroke. Thus, in the present study, these FA and histological results on white matter may coincide with the increased functional deficits after stroke in diabetic patients and rats,[3,6] since white matter plays a pivotal role in neurological functions.

Summary

In the present study, measurements based on T2 maps demonstrate no significant difference of ischemic lesion volumes between T2DM and WT rats in 5w weeks after stroke, using a suture 2h occlusion and reperfusion stroke model and a low dose Streptozotocin injection combined with a high fat food diet diabetic model of young adult Wistar rats. However, compared with WT rats, Gd-DTPA leakage measured by CE-T1WI indicates that T2DM

rats suffered more severe BBB disruption from 1 to 5 weeks after stroke ($p<0.005$), and SWI identified significant larger hemorrhagic volumes in T2DM rats throughout 5w after stroke ($p<0.05$). FA values of ischemic boundary in the striatum were consistently lower in the T2DM rats than in the WT controls, which suggest that T2DM hampers axonal density increase. MRI results were consistent with histological measurements.

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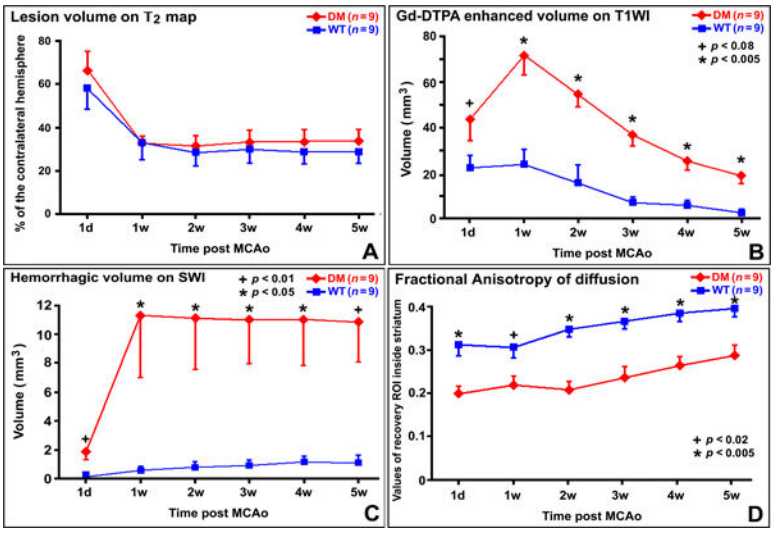

Fig. 1.

The ischemic lesion volumes quantitatively measured by T2 maps (A) did not exhibited any significant differences ($p>0.05$) from 1d to 5w after stroke between the T2DM and WT rats. BBB disruption volumes of Gd-DTPA enhancement with CE-T1WI were significantly larger in the T2DM rats than that in the WT rats from 1w to 5w after stroke (B). SWI measurements of hemorrhagic volumes (C) demonstrated that the T2DM rats significantly exhibited more severe hemorrhage in 5 weeks after stroke than the WT ones. Diffusion FA values were measured significantly higher (D) in WT rats than in T2DM rats after stroke.

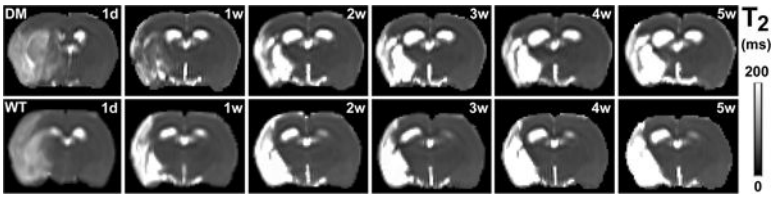

Fig. 2.

MRI T2 maps, from the representative T2DM (upper row) and WT (lower row) rats after stroke, demonstrated the typical evolutions of the ischemic neuronal damage.

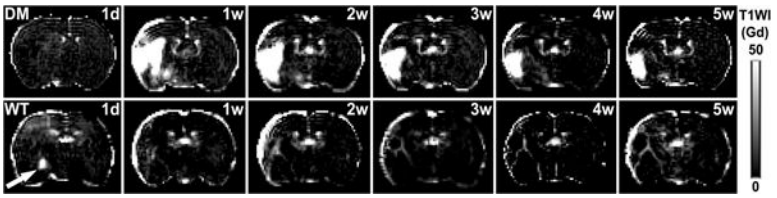

Fig. 3.

BBB disruption with Gd-DTPA enhancement in the subtracted images of CE-T1WI persisted from 1w to 5w post stroke in the T2DM rat (upper row). In contrast, the hyperintensity regions exhibited only at 1 day (arrow) after stroke in the WT rat (lower row), which indicated much less severe BBB disruption.

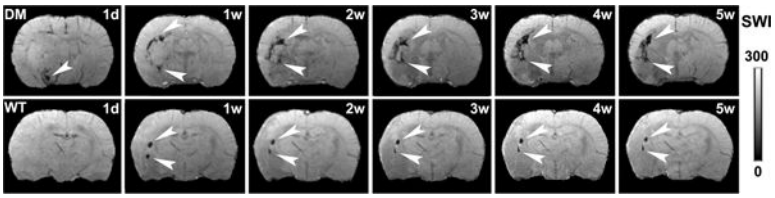

Fig. 4.

The evolutions of hemorrhage after ischemia were demonstrated in SWI images for the representative T2DM (upper row) and WT (lower row) rats, respectively. Hemorrhagic spots (arrow heads) were larger and changeable during 1d to 5w after stroke in the T2DM rat, while smaller and unchanged hemorrhagic spots were identified in the WT rat.

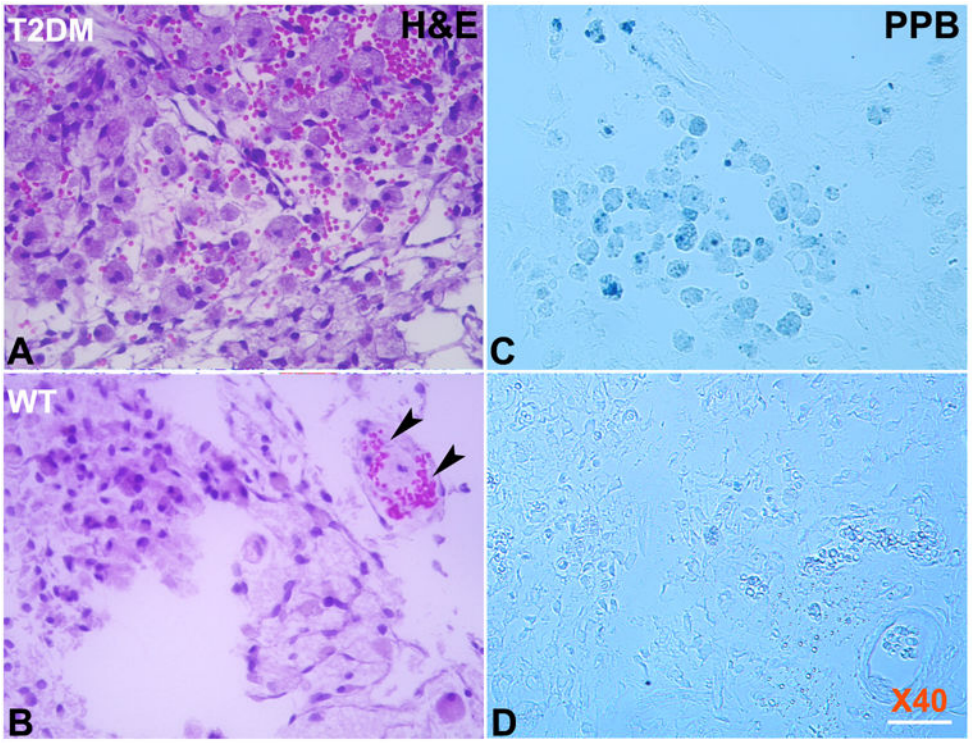

Fig. 5.

With the histological H&E sections under light microscope, the red cells can be found diffusively in the ischemic cerebral tissue in the T2DM rat (everywhere in A, 40×), while the red cells appeared in a relative restrictive and smaller region in the WT rat (black arrow head in B, 40×). PPB stain demonstrated that the blue spots outside of vascular vessels in the brain parenchymal tissue for the T2DM rat (C, 40×) were more in number, larger in size and darker in color than those for the WT rat (D, 40×). Bars in D: 40μm.