The extent of cerebral collateralization directly contributes to the cerebrovascular reserve capacity, which in turn affects the hemodynamics. By the same token, cerebral collateral circulation has long been reported to alter the risk of stroke. In particular, among patients with chronic occlusion of the internal carotid artery (ICA) or arteries, failure of collateralization may contribute to hemodynamic compromise and increased risk of stroke or transient ischemic attacks. In addition, an absence of collateral circulation in the middle cerebral artery (MCA) is associated with a poor prognosis in symptomatic unilateral carotid occlusion. Furthermore, patients with metabolic syndromes are associated with poor anatomic collateral status during acute ischemic stroke. While corroborating experimental evidence suggests that type 2 diabetes mellitus (T2DM) is associated with impaired leptomeningeal collateral compensation during MCA stroke, it remains to be determined whether and to what extent an impaired cerebral collateral flow regulation occurs during carotid occlusion in subjects with T2DM.

**Background and Purpose**—The presence of collaterals is associated with a reduced risk of stroke and transient ischemic attack in patients with steno-occlusive carotid artery disease. Although metabolic syndrome negatively impacts collateral status, it is unclear whether and to what extent type 2 diabetes mellitus affects cerebral collateral flow regulation during hypoperfusion.

**Methods**—We examined the spatial and temporal changes of the leptomeningeal collateral flow and the flow dynamics of the penetrating arterioles in the distal middle cerebral artery and anterior cerebral artery branches over 2 weeks after unilateral common carotid artery occlusion (CCAO) using optical coherent tomography in db/+ and db/db mice. We also assessed the temporal adaptation of the circle of Willis after CCAO by measuring circle of Willis vessel diameters.

**Results**—After unilateral CCAO, db/db mice exhibited diminished leptomeningeal collateral flow compensation compared with db/+ mice, which coincided with a reduced dilation of distal anterior cerebral artery branches, leading to reduced flow not only in pial vessels but also in penetrating arterioles bordering the distal middle cerebral artery and anterior cerebral artery. However, no apparent cell death was detected in either strain of mice during the first week after CCAO. db/db mice also experienced a more severe early reduction in the vessel diameters of several ipsilateral main feeding arteries in the circle of Willis, in addition to a delayed post-CCAO adaptive response by 1 to 2 weeks, compared with db/+ mice.

**Conclusions**—Type 2 diabetes mellitus is an additional risk factor for hemodynamic compromise during cerebral hypoperfusion, which may increase the severity and the risk of stroke or transient ischemic attack. (Stroke. 2016;47:3014-3021. DOI: 10.1161/STROKEAHA.116.014882.)

**Key Words:** anastomosis arteriogenesis carotid occlusive disease CCAO doppler OCT vascular remodeling

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artery (ACA) after unilateral common carotid artery occlusion (CCAO) using optical coherent tomography–based microangiography, and temporal changes in the diameters of the vessels forming the circle of Willis (CW) in normal and diabetic mice. Our results indicate that on unilateral CCAO, diabetic mice experienced an impairment of flow compensation in the leptomeningeal collateral circulation, a more marked reduction of blood flow in the cortical penetrating arterioles bordering the MCA and ACA, and a delay in the adaptation of the CW, contributing to increased hemodynamic compromise and potentiating the risk of stroke or transient ischemic attack.

Materials and Methods

Animals and Housing

This study was approved by the San Francisco VAMC Animal Care and Use Committee. The db/db mouse (B6.BKS(D)-Lepr<db/db>) carrying a mutation in the leptin receptor gene is a well-established rodent model of obesity-induced T2DM.10 Heterozygous db/+ (B6.BKS(D)-Lepr<db/+>) mice were chosen as the normoglycemic controls because of the closer genetic background and a nearly identical cerebrovascular anatomy of the former compared with the db/db mice.11 Male db/dbs and db/+ mice (16–20 weeks old; Jackson Laboratories, ME) were housed 4 per cage on a 12-hour dark/ light cycle with access to food and water ad libitum. Because of the contribution of sex hormone in vascular reactivity, the current study is focused on the male sex. All procedures and analyses were conducted by examiners blinded to experimental conditions.

Unilateral CCAO

The left CCA was permanently occluded with a 6-0 suture to mimic the hypoperfusion state in the human carotid artery occlusion under isoflurane anesthesia. CCAO was chosen over the ICA occlusion model because of technical challenge associated with the latter if performed when the animal is on its prone position with the head fixed on a stereotaxic frame during blood flow imaging.

Blood Flow Imaging Using Doppler Optical Coherent Tomography and OCT-Based Microangiography

Doppler optical coherent tomography (OCT) and OCT-based microangiography (OMAG) imaging was conducted under isoflurane anesthesia through an intact skull at baseline immediately or 1, 7, and 14 days after unilateral CCAO.12 A fiber-based spectral domain OCT system using a superluminescent diode (Thorlabs Inc, Newton, NJ) as the light source was used to image blood flow, providing an ≈14 μm axial resolution in the air.11 In the sample arm, a 5x scan lens (Thorlabs Inc) was used to achieve ≈14 μm lateral resolution with 270 μm depth of field. The line-scan camera (1024 pixel detector-array; Goodrich Inc, Princeton, NJ) was used in the spectrometer with 92 kHz line rate. To image the microvasculature, the scanning produced 400 A lines, covering a distance of ≈2 mm that formed each B frame (in fast-scanning axis). In the slow axis (C scan), it comprised 400 steps, also covering a distance of ≈2 mm. At each step, B frames were repeated 8 times. The final data cube of a 3D scan was composed of 1024×400×3200 (z–x–y) voxels, which took ≈18 s to acquire, with an imaging rate of 180 Hz. After data acquisition, an eigenvalue decomposition-based clutter filtering algorithm12 was used to generate OMAG images from the 8 repeated B frames, producing a final volumetric vascular image of 1024×400×600 (z–x–y) voxels.

After the OMAG scan, a Doppler OMAG scanning was performed covering the same area to obtain the axial red blood cell velocity map within the cortex.13 In contrast to the OMAG protocol, each B scan in the Doppler OMAG protocol consisted of 10,000 A lines by acquiring 25 A lines at each 400 discrete steps. In the slow scan direction (C scan), there were 600 discrete steps, that is, 600 B scans. The data cube of each processed 3D vascular image was composed of 1024×400×600 (z–x–y) voxels, which took ≈100 s to acquire with 6 Hz imaging speed.

Doppler processing of complex signals was applied among A lines in each step by using 3 A-line intervals to have an axial velocity range of ±6.1 mm/s. A phase variance mask was then used to segment meaningful Doppler flow signals from the background.13 The blood flow in the penetrating arterioles was quantified by integrating axial velocity signals corresponding to these vessels in en face Doppler OMAG images.11 The total blood flow in penetrating arterioles per data was estimated by averaging 15 data points from en face Doppler OMAG images at various depths. Because of progressively increased noise caused by scar tissue that appeared to interfere more so with the processing of penetrating arterioles than the pial arteries, we quantified the longitudinal data up to 7-day and 14-day time points for each, respectively. Data from one db/+ and one db/db mouse each were excluded because of incomplete data collection for all required time points.

Quantification of Anastomosis Shift

At baseline and after CCAO, the anastomosis points were marked in each baseline Doppler OCT image where the flow direction has come to an equilibrium, shown as the green to black transition in distal ACAs. The relative distance of anastomosis shift after CCAO was measured by tracing the distance of retrograde flow in the distal ACA comparing to the anastomosis points at baseline using the Image J software with magnified images. The absolute distance was determined by calibrating the pixel value with the known tile dimension of 2 mm.

Quantification of Arterial Diameters in the Primary Collateral Circulation

To assess temporal adaptation after unilateral CCAO, the diameter of the vessels forming the CW and posterior circulation was measured using Image J from the montage images with Dil labeling as described previously.14 The vessels measured include the ICA, MCA, ACA, distal part of ACA (proximal to ophthalmic artery), posterior cerebral artery (PCA), posterior communicating artery, basilar artery (BA), and vertebral artery. The diameter was determined according to the line perpendicular to the main direction of flow at the truncal locations. Specifically, ICA and BA were measured at the terminal portion, while MCA and ACA at the origin before the bifurcation. The proximal ophthalmic artery was measured at the largest point in diameter between the origin of ACA from the point where the ophthalmic artery branched out. The diameter of PCA or posterior communicating artery was determined at the largest point of each vessel near the origin of PCA at which the posterior communicating artery flow joints, while vertebral artery at the vertebro-basilar junction.

Fluoro-Jade C Staining

Degenerating neurons were labeled by Fluoro-Jade C as previously described.15 In brief, brain sections were treated with 1% sodium hydroxide/80% ethanol and 0.06% potassium permanganate, stained in 0.0001% Fluoro-Jade C (Histo-Chem Inc, Jefferson, AR) and coveredslipped with DPX (Sigma). The staining results were visualized and imaged with a Zeiss AxioScope II epifluorescence microscope using an FITC filter.

Statistical Analysis

Data were expressed as mean±SEM and analyzed by 1-way and 2-way ANOVA or 1-way repeated-measures ANOVA using StatView (SAS Institute, Cary, NC) with Bonferroni corrections for multiple comparisons when appropriate. P values <0.05 were considered significant.

Results

Db/db Mice Exhibit Impaired Leptomeningeal Collateral Flow Compensation After Carotid Occlusion

To determine whether T2DM is associated with impaired collateral flow compensation on unilateral CCAO, we investigated the flow characteristics in the leptomeningeal circulation. To

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increase the accuracy of comparison, distal MCA branches were categorized according to branching order, with S1 most proximal to ACA while most distal to MCA. There was no significant difference in baseline flow velocity, diameter, and flux in the distal MCA or ACA segments determined between the 2 genotypes (Figure 1). Immediately after CCAO, a minor shift of the anastomosis point toward distal MCA was detected in the db/+ mice by Doppler OCT, averaging a distance of ≈0.9 mm. This shift of anastomosis points was sustained at 24 hours and 7 days after CCAO in the db/+ mice. In contrast, there was a significantly smaller retrograde shift of anastomosis points in the db/db mice at all time points investigated (Figure 1A and 1C), suggesting an impairment in collateral compensation in the diabetic mice. The vessel diameters of distal ACA and S1 of MCA were greater in the db/+ mice compared with the db/db mice after CCAO, leading to greater flux. There was a tendency for db/+ mice to have a greater flow velocity at S1 after CCAO compared with db/db mice, but the difference did not reach statistical significance. The data suggest that retrograde blood filling in the distal S1 segment of the MCA from the distal ACA via the leptomeningeal anastomoses showed greater reduction in db/db compared with db/+ mice after CCAO (Figure 1).

**db/db Mice Sustain a Persistent Reduction of Blood Flow in the Penetrating Arterioles After CCAO in the Distal MCA and ACA Territories**

Because penetrating arterioles are bottlenecks in the perfusion of the neocortex from the pial vessel network to the subsurface cortical microcirculation, we next determined the changes of blood flow dynamics in the penetrating arteriole in response to CCAO at distal ACA and MCA segments (Figure 2A). Because there was also no significant difference in total flow or in axial velocity for the penetrating arterioles at baseline between genotypes, we expressed the flow dynamics data as percent change over baseline values. The total blood flow in penetrating arterioles increased significantly at 7 days after CCAO in the db/+ mice, whereas it decreased immediately after CCAO and never recovered the following week in the db/db mice (Figure 2B). There was a significant difference in the total blood flow in the penetrating arterioles in the region of interest over 1 week between 2 genotypes of mice (repeated-measures ANOVA: \( F_{3,24} = 3.5; P < 0.05 \)). Although the mean axial velocity of red blood cells passing through penetrating arterioles in db/+ mice was increased gradually after CCAO, there was no overall difference in flow velocity between db/+ and db/db mice at all 3 time points (Figure 2C). Our data suggest that db/db mice may have a greater overall reduction of blood flow into the parenchyma at the border zone of the MCA and ACA.

Although human ICA stenosis or occlusion is often associated with border zone infarct, we did not detect any apparent cell death in the forebrain, including in regions bordering the MCA and ACA in either strain of mice by Fluoro-Jade C staining during the first week after CCAO (Figure 3), suggesting that the degree of hemodynamic ischemia resulting from unilateral CCAO is relatively mild.
CW of db/db Mice Displays a Delayed Adaptation in Response to CCAO

To characterize the temporal adaptation of the CW after unilateral CCAO, we examined the diameter of the major arteries labeled with Dil (Figure 4A) at baseline and 1, 7, and 14 days after CCAO. There was no significant difference found in diameter between baseline and any given time point after CCAO of the CW arteries of the contralateral hemisphere in either genotype (Figure 4C). db/+ mice experienced a significant but only temporary decrease in the ipsilateral PCA diameter 1 day after CCAO, whereas a significant increase in the proximal olfactory artery and BA diameters was found on day 14. The recovery of the ICA in db/+ mice began even earlier on day 7 and persisted through day 14 (Figure 4B and 4C). db/db mice showed a significant but only temporary decrease in the ipsilateral PCA diameter 1 day after CCAO, whereas a significant increase in the proximal olfactory artery and BA diameters was found on day 14. The recovery of the ICA in db/+ mice began even earlier on day 7 and persisted through day 14 (Figure 4B and 4C). db/db mice showed an early and significant narrowing of the ICA and PCA, and only the former had significant recovery and growth by day 14. In general, the mean diameters of the ipsilateral ICA and PCA had decreased by 20% the day after CCAO in db/db mice, yet they were not restored to baseline size until at least 1 week later. This disparity in the major arterial response to unilateral CCAO resulted in significantly smaller truncal diameters in the ICA, MCA, and BA on day 1 and the PCA on day 7 in db/db mice compared with db/+ mice, pointing to an impairment in flow compensation via the CW in the diabetic mice. Except for the BA, all other major arteries in the CW of db/db mice had recovered in vessel size by day 14 (Figure 4C). The diameter of the Pcom is variable, indicating a large biological variance in Pcom patency or configuration among mice.

Discussion

Although experimental and clinical data suggest that metabolic syndrome is associated with poor anatomic collateral status during acute ischemic stroke, it is unclear how and to what extent the collateral flow is affected temporally after chronic cerebral hypoperfusion. On unilateral CCAO resulting in hemodynamic impairment resembling human carotid disease, we found that the db/db mice not only experienced a more severe early reduction in the vessel diameters of the ipsilateral main feeding arteries in the CW, including the ICA, MCA, and PCA compared with db/+ mice, but also a

Figure 1 Continued. a minor shift of the anastomosis point toward distal MCAs, was detected in the normoglycemic db/+ mice by DOCT and sustained at all time points investigated after CCAO. Yellow and blue arrows indicated the various anastomoses points as numbered before and after the shift, respectively. Compared with db/+ mice, db/db mice showed significantly reduced retrograde shift toward distal MCAs. Scale bar: 1 mm. B, Measurement of the average shift of anastomoses points after CCAO compared with those at baseline in each strain. The average shift of anastomoses points toward distal MCA is significantly longer in the db/+ compared with db/db mice at all time points after CCAO. C, Quantification of temporal flow characteristics indicated that there was no significant difference in flow velocity, diameter, or red blood cell (RBC) flux (flux=vπR²) between db/+ and db/db mice at baseline in distal ACA and the 3 segments of distal MCA (S1, S2, and S3, with S1 most distal to MCA). After CCAO, flow velocity decreased in S1 and S2 of MCA, and the direction of flow was reversed at S1 in both strains. After CCAO, db/+ mice showed significant higher retrograde flow velocity at S1, greater vessel diameter, as well as flux at distal ACA and S1 compared with db/db mice. These findings suggest that the db/db mice had diminished leptomeningeal collateral flow compensation during chronic hypoperfusion compared with db/+ mice. N=5/group. *P<0.05; **P<0.01; ***P<0.005; ****P<0.001.
delayed post-CCAO adaptation by 1 to 2 weeks, suggesting that the db/db mice may have a more severe hemodynamic compromise as a consequence. Additionally, in contrast to their normoglycemic counterparts, the db/db mice were less capable of equalizing the perfusion deficit in the distal MCAs by dilating the distal ACAs acutely after unilateral CCAO, leading to reduced flow in the border zone of the distal MCAs. The deficit in flow compensation in the pial collaterals also propagated to a persistent reduction of blood flow in the penetrating arterioles in the distal MCA and ACA territories, potentiating chronic perfusion deficiency in the parenchyma. Unexpectedly, the diminished pial collateral compensation and the perfusion deficiency in the penetrating arterioles of the diabetic mice did not result in apparent cell loss in brain regions bordering the distal MCA and ACA, suggesting that the subacute effect of hypoperfusion induced by CCAO was mild. However, the long-term effect of CCAO-induced low perfusion has not been determined.

Symptomatic carotid occlusion in humans has an annual ischemic stroke risk of 5.5% to 10% that is partially attributable to severely decreased vasodilatory capacity or hemodynamic compromise that is often accompanied by increased oxygen extraction fraction. However, among patients with symptomatic severe ICA stenosis, the risk at 2 years of stroke or transient ischemic attack is significantly reduced among those with angiographically defined collaterals compared with those without, proposing a role of collateralization in reducing stroke risk. Unilateral CCAO is associated with a decrease in cerebral blood flow in the MCA territory in rodents, which can trigger retrograde compensation from the ACA network. Our data suggest that the greater cerebral perfusion pressure drop in the distal MCA relative to ACA branches on unilateral CCAO triggered an immediate shift of the stagnation points of the leptomeningeal anastomoses in the db/+ mice, attempting to equalize perfusion pressure in the border zone between the 2 vascular territories. This immediate retrograde shift of leptomeningeal anastomosis points in the db/+ mice was likely enabled via the dilation of distal ACA branches signaled by fluid shear stress–induced nitric oxide release, leading to increased flow

Figure 2. Blood flow dynamics in the penetrating arterioles within the distal middle cerebral artery (MCA) territory. A, Representative Doppler optical coherent tomography (DOCT) images at baseline and after common carotid artery occlusion (CCAO) similar to Figure 1. The blue rectangles define the region of interest for the analysis of flow dynamics of the penetrating arterioles. Scale bar, 1 mm. B, Total blood flow changes after CCAO for various time points compared with baseline. db/db mice had significantly reduced total blood flow in the penetrating arterioles after CCAO at the time points indicated relative to baseline. *P<0.05. C, There was no significant difference in mean axial velocity changes between db/+ and db/db mice at any time point investigated. N=5/group.
volume or velocity toward the MCA direction. Our data indicate that the inability in retrograde compensation of the distal MCA pial vessels in the db/db mice also resulted in a persistent reduction of blood flow in the penetrating arterioles beneath.

The mechanism that led to the impaired retrograde compensation of pial vessel after brain ischemia is not entirely clear. A recent report suggests that elevation of intracranial pressure after stroke may explain reduced flow through collateral vessels and penetrating arterioles they supply.\textsuperscript{19} However, the impaired shift of the anastomosis points in the db/db mice after CCAO is unlikely because of increased intracranial pressure in the diabetic mice as it occurred almost instantaneously. Rather, it could result from altered myogenic tone and cerebrovascular reactivity.\textsuperscript{20,21} One potential mechanism of endothelial regulation of vascular tone is through nitric oxide because defective nitric oxide signaling in the diabetic mice was suggested by an earlier report, in which the phosphomimetic knock in of the endothelial NO synthase restored vasodilation in the \textit{db/db} mice.\textsuperscript{22} Besides, being chronically hypertensive as in the \textit{db/db} mice causes endothelial damage that may also lead to collateral impairment.\textsuperscript{23} It is unlikely that the db/db mice had a smaller cerebral perfusion deficit between distal MCAs and ACAs compared with db/+ mice, considering the greater reduction of anterograde flow to MCA compared with ACA as suggested by the significantly reduced truncal diameter at MCA compared with ACA ipsilateral to CCAO in the former. Although the diameters of the ipsilateral ACA and MCA main trunks have recovered 2 weeks after CCAO to the size of baseline in the \textit{db/db} mice and, hence, the amount of anterograde flow, those of the distal ACA and MCA S1 still remained smaller compared with \textit{db/+} mice, reiterating the presence of other vascular or nonvascular factors contributing to the impaired flow in the distal ACAs and MCAs and downstream penetrating arterioles in the \textit{db/db} mice.

Consistent with our finding, a recent mouse model of bilateral chronic carotid stenosis using a steel coil also detected an immediate reduction of cortical blood flow on the induction of bilateral CCA stenosis by OCT microangiography, followed by a gradual recovery of flow over the next 27 days.\textsuperscript{24} There was no significant decrease in the size of ACA or proximal olfactory artery ipsilateral to occlusion in either strain at 1 day after CCAO in our study, suggesting the existence of collateral compensation in the anterior circulation likely via cross flow from the contralateral ICA and azygous ACA (murine equivalent of Acom). The flow compensation in the posterior circulation appeared to be less efficient, as evidenced by the immediate reduction of ipsilateral PCA diameter in both strains, although PCA–MCA pial anastomoses were not directly examined in this study. However, animal models of human diseases are prone to limitations. For example, the change of blood flow and vessel diameter in our study reflects rapid response to unilateral CCAO, which is the major limitation of this model of chronic hypoperfusion. Unlike the experimental models of complete or partial occlusion of the carotid artery unilaterally or bilaterally, human chronic hypoperfusion occurs over years to decades, which may induce slow adaptation of the collateral circulation both at the level of CW and leptomeningeal collaterals. Considering the fact that both anatomic and functional configuration of the CW reflects the severity of carotid occlusion,\textsuperscript{25} another limitation of our model is the lack of genetic variance in the structure of collateral vessels, which often exists in the CW in humans. Furthermore, tandem lesions cause not only a higher risk but also lead to poor stroke outcome among patients with carotid stenosis because of increased hemodynamic impairment, which is not captured in the current mouse model of CCAO. On the other hand, being obese and hyperglycemic, the \textit{db/db} mouse is a good animal model for the obese variant of T2DM and insulin resistance.\textsuperscript{18} More importantly, the \textit{db/db} strain also suffers from hypertension and elevated total cholesterol levels, bearing the hallmarks of metabolic syndrome\textsuperscript{26,27} that is associated with a poor collateral status in humans.\textsuperscript{7} However, monogenic mutation in the leptin receptor, as in the \textit{db/db} mice, is rare

\begin{figure}[ht]
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\includegraphics[width=\textwidth]{figure3}
\caption{Representative images of Fluoro-Jade C staining at 24 hours, 4 days, and 7 days after left common carotid artery occlusion (CCAO). There was no apparent cell death at the border zone area of left cortex in either \textit{db/+} or \textit{db/db} mice at any above time point, in contrast to many Fluoro-Jade C-labeled degenerating neurons seen 4 days after distal middle cerebral artery occlusion (MCAO). Scale bars: 100 $\mu$m (left) and 25 $\mu$m (high magnification). N=6/group.}
\end{figure}
in the human population. Thus, future studies are warranted to confirm the hemodynamic changes observed in the current study with other models that cover the diversity seen in human diabetic patients.

Apart from the limitations of the animal model used for this study as described earlier, there also exists potential methodological or technical confounds. Similar to many animal studies of blood flow, our CCAO surgery and OCT imaging was conducted under isoflurane, a potent systemic vasodilator. Long-term metabolic stress, such as T2DM, is known to alter adrenergic receptor function, and a recent report suggests that isoflurane anesthesia may impair cardiovascular function in the Zucker type 2 diabetic rats. Isoflurane could exert a differential effect on hemodynamics in the db/db mice relative to db/+ mice during our study. Finally, measurement of vessel diameter post mortem does not reflect in vivo dynamic remodeling of the vessel, nor does it provide information in flow volume and velocity.

In summary, our results indicate that immediately on unilateral CCAO, in contrast to db/+ mice, db/db mice were less able to dilate distal ACAs to equalize the perfusion deficit in the distal MCA branches, as reflected by a lesser retrograde shifting of flow direction toward the MCA territory and possibly resulting in a greater perfusion deficit in the penetrating arterioles. Several major vessels forming the CW of db/db mice, including the ICA and MCA, also experienced delayed
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dilation compared with those of db/+ mice in the weeks after CCAO. Our data suggest that T2DM is an additional risk factor for hemodynamic compromise during cerebral hypoperfusion, which may increase the severity and the risk of stroke or transient ischemic attack.

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Disclosures

None.

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Impaired Collateral Flow Compensation During Chronic Cerebral Hypoperfusion in the Type 2 Diabetic Mice

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