Comparison of symptomatic vertebrobasilar plaques between patients with and without Diabetes Mellitus using computed tomographic angiography and vessel wall magnetic resonance imaging

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Abstract

Objectives: Diabetes mellitus is significantly associated with posterior circulation ischemic stroke. We aimed to compare the characteristics of vertebrobasilar plaques in symptomatic patients with and without diabetes using high-resolution vessel wall magnetic resonance imaging and computed tomographic angiography.

Methods: From April 2017 to May 2021, cases from patients with transient ischemic attack or stroke in the posterior circulation territory who underwent high-resolution vessel wall magnetic resonance imaging and computed tomographic angiography were reviewed. Characteristics of culprit vertebrobasilar plaques were compared between patients with and without diabetes. Multivariate regression analysis was performed to assess the correlation between culprit plaque characteristics and diabetes.

Results: A total of 148 patients were included and 75 patients were diagnosed with diabetes mellitus. Patients with diabetes had more intraplaque hemorrhage, calcification, spotty calcification presence, and higher calcification volume (all \( p < 0.05 \)) compared with those without diabetes. Multivariate analysis demonstrated differences in the presence of intraplaque hemorrhage (\( p = 0.045 \)) and number of spotty calcifications (\( p = 0.047 \)) were statistically significant after adjusting for baseline characteristics.

Conclusions: Symptomatic patients with diabetes have a higher incidence of intraplaque hemorrhage and larger calcification burden than those without diabetes, indicating the association of diabetes with more advanced plaque features in the posterior circulation.

Keywords
Atherosclerosis, diabetes mellitus, computed tomography angiography, magnetic resonance imaging

Key messages
1. Patients with diabetes had different plaque characteristics in the vertebrobasilar artery compared with those without diabetes.
2. Poorly glycemia-controlled diabetic patients had a higher incidence of IPH presence in the vertebrobasilar artery.
3. A combination of HR-VWI and CTA could provide complementary value in plaque assessment.

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Introduction

Approximately one-fifth of all strokes and transient ischemic attacks affected posterior circulation, supplied by the vertebrobasilar artery system. Diabetes mellitus (DM) is preferentially associated with an increased risk of stroke in the posterior circulation. Large artery atherosclerosis is the major cause of morbidity and mortality in DM patients. Increasing studies suggested the susceptibility of vertebrobasilar circulation in DM may contribute to the location-specific discrepancy in the development of atherosclerosis and occurrence of ischemic stroke.

Previous studies reported DM-specific atherosclerotic patterns in various extracranial arterial beds. Pathology study suggested DM may increase inflammation and neovascularization, contributing to the development of intraplaque hemorrhage (IPH) in human diabetic atherosclerosis. High-resolution vessel wall magnetic resonance imaging (HR-VWI) allows for identification of high-risk plaque features including IPH and plaque enhancement, and provides reliable assessment of plaque morphology. These HR-VWI defined plaque characteristics may be responsible for the occurrence of cerebrovascular events and predict the etiologies of stroke.

Complementary to HR-VWI, computed tomographic angiography (CTA) could provide incremental value in the assessment of plaque vulnerability and enable the quantification of vascular calcification. In contrast to the intracranial internal carotid artery, calcification of the vertebrobasilar artery was mainly found in the elderly and highly correlated with luminal stenosis, indicating its atherosclerotic origin. The amount and pattern of calcification have been reported to predict different risks of cardiovascular events. Spotty calcification was recognized as a feature of culprit coronary lesion and associated with plaque progression.

Given this background, we aimed to compare the differences in vertebrobasilar plaque features of DM patients with non-DM patients using a multi-modality imaging approach.

Methods

Study patients

From April 2017 to June 2021, all patients in our database who underwent both high-resolution vessel wall magnetic resonance imaging (HR-VWI) and computed tomographic angiography (CTA) were retrospectively reviewed. The inclusion criteria were as followed: (1) presence of transient ischemic attack (TIA) or stroke in the territory of posterior circulation based on neurological examination or diffusion-weighted imaging (DWI); (2) baseline imaging included HR-VWI and CTA examinations within a time interval of 4 weeks after the onset of neurological symptoms; and (3) patients older than 18 years. Exclusion criteria consisted of (i) posterior circulation large vessel occlusion, (ii) evidence of non-atherosclerotic intracranial vascular pathology (e.g., dissection, reversible cerebral vasospasmodic syndrome, and aneurysm). The neuroimaging diagnosis of vertebrobasilar artery dissection included intimal flap, double lumen, intramural hematoma, aneurysmal dilatation, or pearl and string sign without any atherosclerotic change of the involved artery based on HR-VWI and/or CTA. The HR-VWI feature of reversible cerebral vasospasmodic syndrome was multiple arterial wall thickenings without or with minimal arterial wall enhancement. (iii) evidence of cardiac sources of emboli, (iv) patients with a history of stent or treatment in the vertebrobasilar artery, (v) poor image quality based on the vessel wall delineation and artifacts, and (vi) insufficient clinical data. This research project was approved by a suitably constituted Ethics Committee of our institution, and it conforms to the provisions of the Declaration of Helsinki.

Patients’ baseline information from medical records was acquired systematically. Diabetes mellitus (DM) was diagnosed based on their blood glucose levels, that is, either a fasting plasma glucose level of ≥7.0 mmol/L or an OGTT result of ≥11.1 mmol/L. The American Diabetes Association recommended the glycated hemoglobin (HbA1c) level of <7% to reduce the microvascular and macrovascular complications. DM patients were divided into two subgroups by the level of HbA1c (≥7.0% as high-HbA1c group vs. <7.0% as low-HbA1c group). The risk of ischemic stroke triples among those with diabetes ≥10 years. DM patients were divided into shorter [0–9 years] and longer [≥10 years] duration groups. Patients were also categorized as acute if they underwent HR-VWI within 4 weeks of the presenting symptoms, subacute if they underwent HR-VWI between 4 and 12 weeks, and chronic if they underwent HR-VWI beyond 12 weeks.

MR imaging examination

All MRI and MRA exams were performed on a 3T MR imaging scanner (Ingenia; Philips Healthcare) with a 16-channel head coil. The standardized imaging protocol included DWI, time-of-flight magnetic resonance angiography (TOF-MRA) or phase-contrast magnetic resonance angiography (PC-MRA), and pre- and post-contrast T1-weighted HR-VWI. The HR-VWI sequence was performed using a volumetric isotropic turbo spin-echo acquisition (VISTA; Philips Healthcare) in coronal and axial planes for comprehensive intracranial artery coverage and optimal blood suppression. The following parameters were used: TR/TE, 425 ms/19 ms; field of view, 220×220 mm; matrix, 316×312; TSE factor, 28 including 2 startup echoes; oversampling factor, 1.3; number of average, 2; SENSE factor, 2; echo spacing, 6.3 ms; acquired resolution, 0.7×0.7×1.1 mm³; and scan time, 6.1 min. HR-VWI images...
were repeated 5 min after contrast administration of 0.1 mmol/kg contrast agent (dimeglumine gadopentetate).

**MR image analysis**

All MR images were reviewed and analyzed using a Picture Archiving and Communication System workstation. Two radiologists who were blinded to the clinical information identified the presence of plaques independently and discrepancies were resolved by consensus. The target of vessel segments included the proximal, middle, and distal portion of basilar artery and V4 of vertebral artery. A culprit plaque was defined as the only or most stenotic lesion arising within the artery territory of ischemic events. The culprit lesions arising in the posterior cerebral artery were excluded. A non-culprit plaque was considered if not the most stenotic lesion or not occurring within the artery territory of ischemic events. Luminal stenosis was measured on pre-contrast T1-weighted images using criteria established in the Warfarin-Aspirin Symptomatic Intracranial Disease trial. Intraplaque hemorrhage (IPH) was defined as hyperintensity within the plaque on the pre-contrast T1-weighted images, higher than 150% of signal intensity of the adjacent brain parenchyma (i.e., white matter). Quantitative measurements were obtained from culprit plaques using medical imaging viewer software, Horos (v. 3.3.6; The Horos Project). Lumen and outer wall contours were manually segmented at the most stenotic slice on pre- and post-contrast T1-weighted images. Plaque morphological measurements included lumen area (LA), outer wall area (OWA), wall area (WA: OWA-LA), normal wall index (NWI: WA/OWA *100%), maximum wall thickness (MaxWT), minimum wall thickness (MinWT), and eccentricity index (EI: (MaxWT-MinWT)/MaxWT). Remodeling index (RI) was calculated as the ratio of the vessel area at the maximal lumen narrowing site to that at the reference site. Plaque contrast-enhancement (%CE) was calculated as (Spost-Spre)/Spre*100%, where Spost and Spre were the signal intensities normalized to the signal intensity of adjacent brain parenchyma using a standard measurement (area of 20 mm²) on post- and pre-contrast T1-weighted images, respectively.

**CTA imaging acquisition**

CTA protocol was conducted on a 128-slice dual-source CT scanner (SOMATOM Definition Flash, Siemens healthiness, Forchheim, Germany). Same reconstruction parameters were used for single-phase CTA and 4D multi-phase CTA (a section thickness of 1.0 mm; an interval of 0.7 mm).
Single phase CTA data were acquired from the aortic arch to the top of the skull in the caudocranial direction. The following acquisition parameters were used: Dual energy mode, with tube voltage, 100 kV and Sn140 kV; reference mAs104, CARE Dose4D on; pitch 0.8; slice acquisition, 128×0.6 mm by using a z-flying focal spot; gantry rotation time, 0.28 s; and field of view, 200–250 mm.

4D multi-phase CTA was acquired from the skull base acquired with 9.6-cm coverage in the z-axis from the skull vertex. The following acquisition parameters were used: tube voltage, 80 kV; tube current, 150 mAs; slice acquisition, 128×0.6 mm by using a z-flying focal spot; gantry rotation time, 0.28 s; and field of view, 200–250 mm. A total of 60 mL or 30 mL of contrast medium (ioversol, 350 mg I/mL, Jiangsu Hengrui Medical Co) was intravenously injected, respectively, followed by 60 mL of saline with the same flow rate. Data acquisition was triggered as soon as the region of interest in the right common carotid artery reached the threshold of 100 Hounsfield units (HU) with single-phase CTA. Pulsed full rotation scan beginning 2s after contrast injection with 19 times scan about 46.35 s was used for 4D multi-phase CTA.

**CTA image analysis**

All CTA images were independently interpreted by two radiologists with a head-to-head comparison with HR-VWI images. A consensus decision was reached by a joint reading. Calcification was defined as the presence of hyperdensity with a CT attenuation of 130 HU or greater. Spotty calcification was defined as a lesion of calcium deposition with a length below 3 mm (extent of the calcification parallel to the course of the vessel) and within an arc of less than 90°.

### Table 2. Comparison of culprit plaque characteristics between patients with DM and without DM.

|                          | DM (n = 75) | Non-DM (n = 73) | p Value |
|--------------------------|-------------|-----------------|---------|
| Plaque location          |             |                 |         |
| Basilar artery           | 28 (37%)    | 33 (45%)        | 0.404   |
| Vertebral artery         | 47 (63%)    | 40 (55%)        |         |
| Stenosis degree, %       | 62.84 ± 10.70 | 62.69 ± 10.48   | 0.929   |
| Category of stenosis     |             |                 |         |
| <50%                     | 7 (10%)     | 8 (11%)         |         |
| 50%–70%                  | 49 (65%)    | 45 (62%)        |         |
| 71%–99%                  | 19 (25%)    | 20 (27%)        |         |
| Plaque area, mm²         | 23.14 ± 9.43 | 23.30 ± 10.20   | 0.923   |
| Normal wall index        | 84.19 ± 8.48 | 83.43 ± 7.71    | 0.572   |
| Contrast enhancement     | 42.36 ± 16.53 | 40.34 ± 16.54   | 0.459   |
| Eccentricity index       | 0.51 ± 0.23 | 0.52 ± 0.23     | 0.984   |
| Remodeling index         | 1.16 ± 0.18 | 1.23 ± 0.44     | 0.181   |
| IPH                      | 26 (35%)    | 3 (18%)         | 0.025*  |
| Calcification            | 47 (63%)    | 32 (44%)        | 0.032*  |
| Spotty calcification     | 33 (44%)    | 20 (27%)        | 0.041*  |
| Number of spotty calcifications (per plaque) | 0 (0.1)     | 0 (0.1)         | 0.036*  |
| Calcification volume, mm³| 6 (0.42)    | 0 (0.13)        | <0.01*  |

DM: diabetes mellitus; IPH: intraplaque hemorrhage. Data are presented as numbers (%), means ± standard deviations, or median (interquartile range). *p< 0.05.

### Statistical analysis

Data were analyzed by using SPSS 26.0 (Chicago, IL, USA). Categorical data were presented as frequencies, and continuous data were presented as means ± standard deviations (SD) or medians and interquartile range (IQR). Comparison of continuous variables was performed using Student’s t-tests or Mann–Whitney U test. Categoric variables were compared using the Chi-square test or Fisher’s exact test, depending on the distribution of the data. Univariate analysis was performed at first to determine the relationship between vertebrobasilar plaque characteristics and the presence of...
DM. Multivariable linear (continuous variables) and logistic regression analysis (categorical variables) were used to correct the variables with $p$-value < 0.2 in univariate analysis. Inter-reader agreements were estimated using the Kappa Value for categorical variables and intraclass correlation coefficient (ICC) for continuous variables. A two-tailed $p$-value < 0.05 was considered statistically significant in all analyses.

**Results**

**Study population**

A total of 148 patients (mean age, 62.50 ± 8.19 years; 54 female) were included in the analysis. Among them, 75 patients (61 ischemic strokes, 14 TIA) were enrolled as DM group and 73 patients (56 ischemic strokes, 17 TIA) as non-DM group. The clinical characteristics in patients with or without DM are summarized in Table 1. DM patients were more likely to have a history of prior stroke (49% vs. 33%, $p = 0.034$) compared to non-DM patients. No significant differences were observed in the clinical risk factors, onset-to-VWI time, and symptom presentation between the two groups.

**Plaque characteristics**

The target vessel was basilar artery in 41% and vertebral artery in 59% of all patients. The distribution of culprit plaques was not different between DM and non-DM patients. Culprit plaque features in patients with or without DM are summarized in Table 2. A total of 94 (64%) plaques were identified with degree of stenosis between 50%-70%. There was no significant difference in the degree of stenosis (62.84± 10.70 vs 62.69± 10.48, $p = 0.929$) between DM and non-DM groups. NWI, CE%, EI, and RI were similar between the two groups. Compared with non-DM patients, DM patients had a higher prevalence of IPH (35% vs. 18%; $p = 0.025$), calcification (63% vs. 44%; $p = 0.032$), spotty calcification (44% vs. 27%; $p = 0.041$), and larger number of spotty calcifications ($p = 0.036$) (Figures 1 and 2). A significant difference was observed as DM patients presented with larger calcification volume than non-DM patients ($p < 0.01$).

**Associations of vertebrobasilar plaque characteristics with the presence of DM**

The uni- and multivariate analyses of the association between plaque characteristics and the presence of DM are shown in Table 3. Multivariable logistic regression model demonstrated that the associations of IPH (OR, 2.40 [95% CI, 1.03 to 5.77], $p = 0.045$) and number of spotty calcifications ($\beta$, 0.37 [95% CI, 0.01 to 0.73], $p = 0.047$) with the presence of DM were statistically significant after adjusting for baseline characteristics. DM was marginally significantly associated with presence of calcification (OR, 1.96 [95% CI,
0.98 to 3.95], \( p = 0.057 \) in the multivariate regression analysis. There were no significant differences in stenosis degree, NWI, RI, EI, and CE% between DM and non-DM patients after multivariate adjustment.

**DM subgroup analysis**

As shown in Table 4, 45 and 30 patients with diabetes were divided into the high- and low-HbA1c groups, respectively. Compared with patients with the low-HbA1c level, patients with the high-HbA1c level demonstrated significantly more presence of IPH (44% vs. 20%, \( p = 0.047 \)). Fifty-five and 20 patients with diabetes were divided into the shorter- and longer-duration groups, respectively. There were no significant differences between the patients with shorter and longer duration of DM.

**Inter-reader reliability**

Inter-reader agreement for presence of IPH (k: 0.860, 95% CI, 0.772–0.948), calcification (k: 0.986, 95% CI, 0.959–1) and spotty calcification (k: 0.848, 95% CI, 0.758–0.938) were good to excellent. Inter-reader reliability for LA (ICC, 0.936; 95% CI, 0.879–0.967), OWA (ICC, 0.905; 95% CI, 0.822–0.950), Max WT (ICC, 0.931; 95% CI, 0.869–0.964) and Min WT (ICC, 0.920; 95% CI, 0.850–0.958) were good to excellent.

**Discussion**

In the present study, DM patients demonstrated a higher prevalence of IPH and spotty calcification presence and larger calcification burden than non-DM patients in the vertebrobasilar artery. Moreover, DM patients with HbA1C ≥7.0% had more IPH presence than those with HbA1C < 7.0%. Our study suggested that DM patients may suffer from more advanced plaque features in the posterior circulation.

In the present study, the head-to-head comparison of CTA and HR-VWI provides a comprehensive characterization of plaque composition and morphology in intracranial atherosclerosis. Our study extends the previous reports that patients with diabetes had different atherosclerotic patterns in various extracranial arterial beds. The diabetic-specific features of plaque vulnerability may indicate the association between DM and its preference for posterior circulation ischemic stroke.

In the present study, culprit plaques in diabetics demonstrated more presence of spotty calcification than those...
in non-diabetics, with an expected increase number of 0.37 per plaque. Hyperglycemia could accelerate inflammation and oxidative stress, promoting plaque calcification in both intima and media.23 Spotty calcification could represent an active state of the dynamic process of atherosclerosis. An intravascular ultrasound imaging study of 1347 patients with stable coronary artery disease reported a higher prevalence of spotty calcification in diabetic patients.15 An intracoronary optical coherence tomography study of 167 patients with a first acute coronary event reported more frequent presence of superficial calcified nodules in diabetic patients.24 Overall, the number of spotty calcifications in the vertebrobasilar artery was relatively paucity, in agreement with the recent case-control study by Zhang et al.25

Increasing evidence showed intracranial artery calcification could be used as an imaging marker to predict postprocedural outcomes after endovascular therapy. Lee et al.26 reported that a high whole-brain calcification burden was associated with poor outcomes after intravenous or intra-arterial revascularization treatment for acute middle cerebral artery trunk occlusion. Two studies reported that calcification volumes of the intracranial carotid artery and vertebrobasilar artery were significantly associated with worse outcomes after intra-arterial revascularization therapies.27,28 Yu et al.29 reported that calcification volume on the lesion side was associated with hemorrhagic transformation after intravenous thrombolysis. Therefore, the higher volume of vertebrobasilar artery calcification observed in DM patients may substantially influence the prognostication and treatment decision-making.

As a recognized high-risk plaque feature, IPH originates from the disruption of incomplete neovessels, aggravated by inflammation. Gao et al.30 reported neovascularization was more frequent in the coronary atherosclerotic lesions of Table 3. Association between vertebrobasilar plaque characteristics and DM.

| Parameter | Univariable | Multivariable |
|-----------|-------------|---------------|
|           | Parameter | 95% CI | p Value | Parameter | 95% CI | p Value |
| Normal wall index | 0.01 | -0.02 to 0.03 | 0.572 | 0.00 | -0.03 to 0.03 | 0.846 |
| Remodeling index | 0.02 | -0.03 to 0.07 | 0.391 | 0.03 | -0.02 to 0.08 | 0.299 |
| Contrast enhancement | 0.02 | -0.03 to 0.07 | 0.459 | 0.01 | -0.05 to 0.07 | 0.719 |
| Presence of IPH | 2.45 | 1.16 to 5.39 | 0.022* | 2.40 | 1.03 to 5.77 | 0.045* |
| Presence of calcification | 2.15 | 1.12 to 4.19 | 0.023* | 1.96 | 0.98 to 3.95 | 0.057 |
| Presence of spotty calcification | 2.08 | 1.05 to 4.19 | 0.036* | 2.05 | 0.98 to 4.40 | 0.060 |
| Number of spotty calcifications (per plaque) | 0.41 | 0.07 to 0.76 | 0.018* | 0.37 | 0.01 to 0.73 | 0.047* |

The multivariate model is adjusted for hyperlipidemia, triglyceride, HDL cholesterol, coronary heart disease and history of stroke. DM: diabetes mellitus; IPH: intraplaque hemorrhage.

Table 4. Comparison of culprit plaque characteristics between patients with different glycemic control and duration of diabetes.

| | Low-HbA1c (<7.0%) | High-HbA1c (≥7.0%) | p Value |
| | (n = 30) | (n = 45) | |
| Stenosis degree | 62.06 ± 12.33 | 64.02 ± 7.70 | 0.441 |
| Normal wall index | 84.96 ± 6.53 | 83.68 ± 9.60 | 0.527 |
| Contrast enhancement | 43.96 ± 15.11 | 41.29 ± 17.51 | 0.497 |
| Eccentricity index | 0.48 ± 0.24 | 0.54 ± 0.22 | 0.3 |
| Remodeling index | 1.16 ± 0.16 | 1.16 ± 0.20 | 0.981 |
| IPH | 6 (20%) | 20 (44%) | 0.047* |
| Calcification | 20 (67%) | 27 (60%) | 0.631 |
| Spotty calcification | 16 (53%) | 17 (38%) | 0.237 |
| Number of spotty calcifications | 1 (0.1) | 0 (0.1) | 0.536 |
| Calcification volume, mm3 | 16 (0.51.75) | 6 (0.31) | 0.205 |

DM: diabetes mellitus; HbA1C: glycated hemoglobin; IPH: intraplaque hemorrhage.

Data are presented as numbers (%), means ± standard deviations, or median (interquartile range).

*p < 0.05.
patients with DM using optical coherence tomography. Han et al. 31 recently demonstrated more IPH presence in femoral arteries of DM patients using vessel wall imaging. In the present study, we found a significantly higher incidence of IPH in patients with diabetes, especially those with poor glycemic control. Our study was in consistent with the pathologic observations reported increased neo-vascularization and IPH grade in diabetic plaques. 32 The higher incidence of IPH in diabetic plaques indicated the vulnerability of posterior circulation to hyperglycemia-induced injuries.

In the present study, no significant differences were found in the degree of contrast enhancement at the culprit lesions between DM and non-DM patients, high- and low-HbA1c DM patients, and shorter- and longer-duration DM patients. Recent studies 33 reported poorly controlled glycemia was strongly associated with strongly enhanced intracranial plaque. However, their results could not be simply compared with ours since we only analyzed the culprit plaques in the posterior circulation. Increased contrast wash-in could be expected as endothelium deficiency after symptoms presentation and greater vasa vasorum density in the vertebrobasilar artery. 34 Calcification exhibited a negative correlation with the entry and delivery of contrast agents into the plaque as validated by histology. 35

Limitations of this study need to be considered. (1) First, this is a retrospective study. The combined performance of CTA and HR-VWI may lead to a selection bias in symptom severity. (2) Future study with a larger sample size is needed to elucidate the association between glycemic control and high-risk plaque features. (3) Some plaques with patent lumen on TOF-MRA in the proximal V4 segment may be missed for the limited field of view. (4) CTA and 4D multi-phase CTA were associated with an elevated radiation dose and administration of contrast media, which was restricted within the retrospective nature of our study design.

Conclusion

The present study demonstrated symptomatic DM patients have more presence of IPH and larger calcification burden in the vertebrobasilar artery plaques than non-DM patients, suggesting patients with diabetes tend to be related with more advanced atherosclerotic diseases. The diabetic-specific features may indicate the association between DM and its preference for posterior circulation ischemic stroke.

Abbreviations

CE = contrast enhancement; CTA = computed tomographic angiography; DM = diabetes mellitus; DWI = diffusion-weighted imaging; EI = eccentricity index; HR-VWI = high-resolution vessel wall magnetic resonance imaging; HU = Hounsfield unit; IPH = intraplaque hemorrhage; LA = lumen area; MaxWT = maximum wall thickness; MinWT = minimum wall thickness; NWI = normal wall index; OWA = outer wall area; PC-MRA = phase-contrast magnetic resonance angiography; PR = positive remodeling; RI = remodeling index; ROI = region of interest; TOF-MRA = time-of-flight magnetic resonance angiography; VISTA = volumetric isotropic turbo spin-echo acquisition; WA = wall area.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Natural Science Foundation of Shandong Province (grant no.ZR2018BH029, ZR2020QH266), National Natural Science Foundation of China (grant no.8200077), and Academic Promotion Programme of Shandong First Medical University (no.2019QL023).

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