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COMMENTARY

Retinopathy: A sign of cerebral small vessel disease in diabetes?

Cardiocerebrovascular disease greatly influences the prognosis of diabetes patients. Silent lacunar infarcts, white matter lesions (WMLs) and cerebral microbleeds are magnetic resonance imaging markers of cerebral small vessel disease (SVD), and as they are associated with stroke and dementia, prevention of their incidence and progression is important in clinical practice. The findings of previous autopsy and clinical studies suggest that lacunar infarcts are more prevalent in diabetes patients. In contrast, the findings of studies on an association between diabetes and WMLs have been inconsistent. Previous studies have also shown an association between retinopathy or chronic kidney disease, and the appearance and progression of SVD[1–3]. This indicates a similarity between the vasculature of the kidney or retina and cerebral penetrating arteries, and has been described as the so-called cerebro–renal interaction and cerebro–retinal interaction, which have been receiving attention. It is possible to observe changes in the retinal vasculature directly by non-invasive procedures, and the early discovery of such changes could indicate the presence of subclinical brain lesions[4]. Thus, understanding the significance of early changes in retinal vessels might help to reduce the development of cerebrovascular disease. In *Diabetes Care*, Sanahuja *et al.*[5] recently investigated the presence and severity of diabetic retinopathy (DR), and its relationship with the presence and severity of cerebral SVD in type 2 diabetes patients with no history of cardiovascular or kidney disease. The current study provides noble insight into the link between the eye and brain in type 2 diabetes.

The authors evaluated 312 type 2 diabetes patients (mean age 57 years, age range 40–75 years) without established impaired renal function (calculated glomerular filtration rate <60 mL/min) and previous cardiovascular disease. Although it has been suggested that albuminuria is associated with WMLs or cerebral microbleeds[3], diabetes patients with microalbuminuria were not included in the present study. Therefore, patients with chronic kidney disease were excluded from the analysis. Retinopathy was classified as four grades according to the International Consensus on Clinical DR: mild non-proliferative, moderate non-proliferative, severe non-proliferative and proliferative. Lacunar infarcts were defined as focal areas (<20 mm in diameter) of decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images using 1.5-T brain magnetic resonance imaging. WMLs were scored according to the age-related white matter changes scale. In the present study, the authors evaluated severity of SVD as SVD score, comprehensive grade of the number of lacunar infarcts and the grade of WMLs. Cerebral microbleeds, a manifestation of SVD, were not evaluated in the present study. A special feature of the present study was that in addition to carrying out head magnetic resonance imaging, the middle cerebral artery (MCA) trunk was visualized by color Doppler using a 2–3-MHz transcranial probe, and pulsatility index (PI) values were evaluated in 70% of the patients. PI values are an indicator of peripheral vascular resistance (diastolic dysfunction), so they are associated with WML severity.

Regarding differences in characteristics between patients with and without DR, for those with DR, the rate of hypertension was higher; measurements for systolic blood pressure, abdominal circumference, glycated hemoglobin and urinary albumin/creatinine ratio were also higher; and more patients with DR were receiving insulin or aspirin treatment. The rate of lacunes and WMLs was not significantly different between patients with DR and those without DR. However, the rate of SVD was higher in patients with DR than in those without DR (42 *vs* 30.1%, $P = 0.04$). Rates for WMLs and SVD were associated with the severity of DR. In contrast, the rate for lacunes was not associated with the severity of DR. A high SVD score was observed in 8.2% of patients without DR and in 18.9% of those with DR ($P < 0.01$), and the score elevated according to the increasing severity of the retinopathy status ($P < 0.01$). In multiple regression analysis, including the presence or degree of retinopathy, only age and systolic blood pressure were independently associated with the presence of SVD. After adjustment for potential variables, including the presence/absence of retinopathy, age and the presence of retinopathy were associated with a high SVD score. The median MCA PI was higher in patients with DR compared with those without DR, and increased gradually with the presence and severity of DR. Furthermore, patients with high SVD scores had significantly higher median MCA PI values than those without SVD or with mild SVD.

The main finding of the current study[5] was that patients with type 2 diabetes and DR, without previous cardiovascular disease, more often had cerebral SVD in contrast to those patients without DR.

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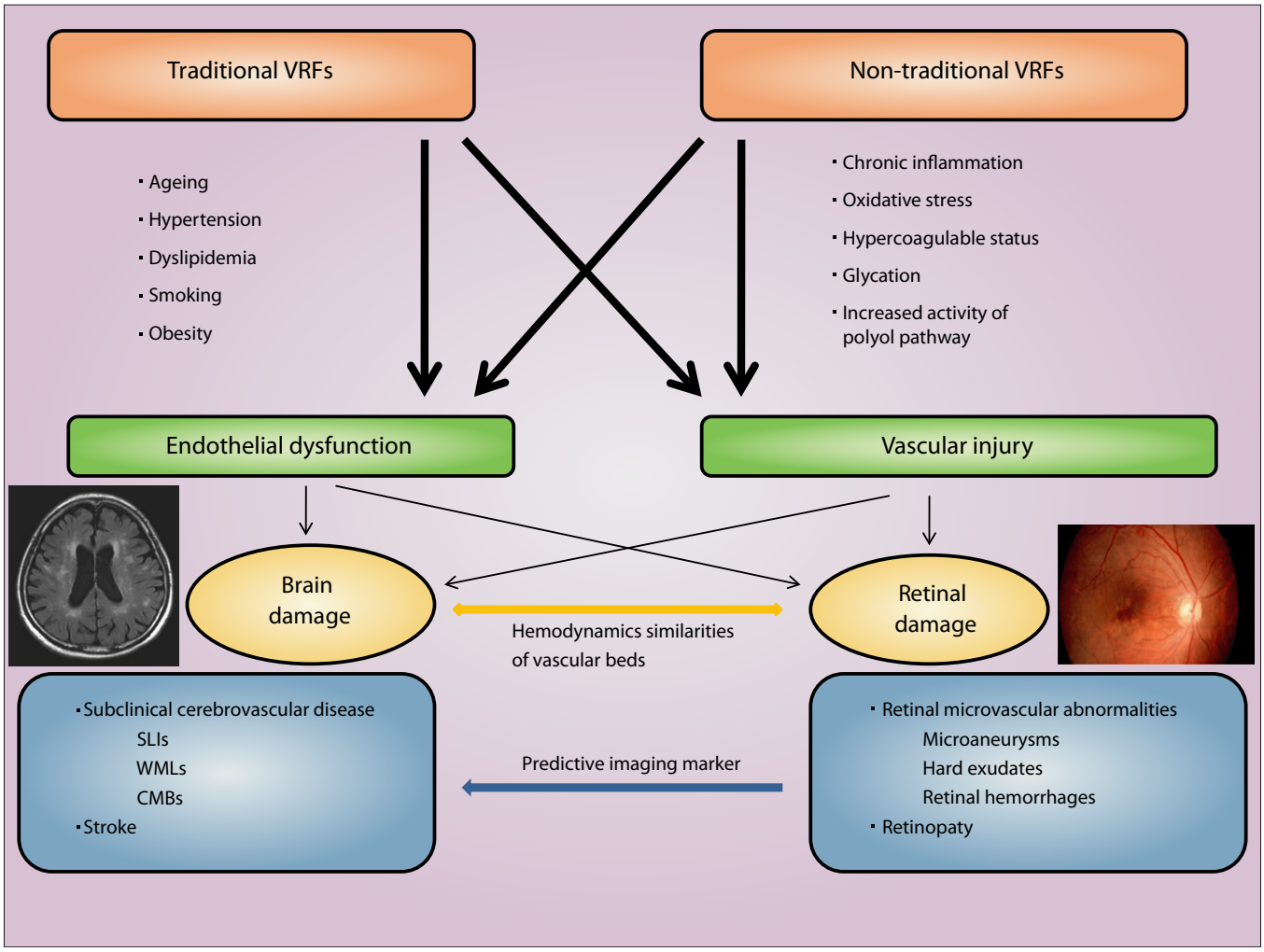

Figure 1 | Schematic representation of cerebro–retinal interaction in patients with type 2 diabetes. It shows a possible link between cerebral and retinal microvascular abnormalities in type 2 diabetes patients. Hemodynamic similarities are observed in the vasculature of the retinal and cerebral penetrating arteries. Retinal microvascular abnormalities might be useful predictive imaging markers for cerebral small vessel disease. CMBs, cerebral microbleeds; SLIs, silent lacunar infarctions; VRFs, vascular risk factors; WMLs, white matter lesions.

Furthermore, patients with advanced grades of DR also had more severe grades of SVD and higher MCA PI values. PI steadily increased according to the presence and degree of DR. These findings show that the prevalence and severity of retinal vascular lesions and cerebral small vessel lesions are mutually linked. Many previous studies have reported associations between decline in estimated glomerular filtration rate or between albuminuria, a marker of endothelial dysfunction, and cerebral SVD[3,4]. It would be very interesting to consider relationships between the vasculature of the kidney and the penetrating branch arteries of the brain, given their similarity[6]. Such relationships might also apply to the vasculatures of the retina and the cerebral penetrating branch arteries. We could speculate that common vascular beds are present in the retina and brain, and that small vessel lesions coexist in them (Figure 1). Furthermore, arterial stiffness is an independent factor for the severity of cerebral WMLs, and DR is independently associated with pulse wave velocity in type 2 diabetes. The clinical implication of the results is interesting, because the investigation of an association between retinopathy and MCA PI values would also lead to an indirect evaluation of cerebral small arterial stiffness. Recently, an association between arterial stiffness and cognitive function has also been suggested[7], and there have been studies that showed an association between diabetic retinopathy and cognitive decline[8,9].

As the present study was a cross-sectional design, it does not show a causal relationship between retinopathy and cerebral SVD. As another limitation, no comparison was made with non-diabetic patients as a control. Furthermore, the

rate of lacunar infarcts was lower than those in previous studies[10], because patients included in the present study were younger (mean age 57 years) than those in previous studies, and had no history of cardiovascular and chronic kidney disease. However, the fact that its findings suggest associations of incidence and severity of retinopathy with prevalence and severity of cerebral SVD in such a population is important. The present study supports the hypothesis that the brain is a target organ for diabetic microangiopathy. Retinal vascular imaging might be useful for further investigation on the pathogenesis and therapeutic strategies for cerebral SVD in diabetes patients.

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REFERENCES

1. Qiu C, Cotch MF, Sigurdsson S, *et al.* Retinal and cerebral microvascular signs and diabetes: the Age, Gene/Environment Susceptibility-Reykjavik Study. *Diabetes* 2008; 57: 1645–1650.
2. Cheung N, Mosley T, Islam A, *et al.* Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study. *Brain* 2010; 133: 1987–1993.
3. Akoudad S, Sedaghat S, Hofman A, *et al.* Kidney function and cerebral small vessel disease in the general population. *Int J Stroke* 2015; 10: 603–608.
4. Umemura T, Kawamura T, Hotta N. Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: a possible link between cerebral and retinal microvascular abnormalities. *J Diabetes Investig* 2017; 8: 134–148.
5. Sanahuja J, Alonso N, Diez J, *et al.* Increased burden of cerebral small vessel disease in patients with type 2 diabetes and retinopathy. *Diabetes Care* 2016; 39: 1614–1620.
6. Ito S, Nagasawa T, Abe M, *et al.* Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res* 2009; 32: 115–121.
7. Hazzouri AZ, Newman AB, Simonsick E, *et al.* Pulse wave velocity and cognitive decline in elders: the Health, Aging, and Body Composition Study. *Stroke* 2013; 44: 388–393.
8. Crosby-Nwaobi RR, Sivaprasad S, Amiel S, *et al.* The relationship between diabetic retinopathy and cognitive impairment. *Diabetes Care* 2013; 36: 3177–3186.
9. Kawamura T, Umemura T, Hotta N. Curious relationship between cognitive impairment and diabetic retinopathy. *J Diabetes Investig* 2015; 6: 21–23.
10. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts; a systematic review. *Lancet Neurol* 2007; 6: 611–619.

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