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EDITORIAL

Diabetes and Stroke

More than just accelerated atherosclerosis?

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مرض السكري والسكتة الدماغية

أكثر من مجرد تسارع تصلب الشرايين؟

أرونوداي جوجار

Both stroke and diabetes mellitus (DM) are increasingly common conditions that contribute to worldwide morbidity and mortality, thus necessitating urgent action. Globally, there were 33 million estimated cases of stroke in 2013, with a loss of 39.4 and 62.8 million disability-adjusted life years (DALYs) due to ischaemic and haemorrhagic stroke, respectively.[1,2] Furthermore, stroke was the second most common cause of death (11.8%) and the third most common cause of disability (4.5%).[2] A systematic review of 64 studies from the Middle East indicated incidence and prevalence rates of 22.7–250 and 508–777 per 100,000 people per year, respectively.[3] Over the next 20 years, stroke-related mortality is predicted to triple in Africa, the Middle East and in Latin American countries.[4] In 2014, an estimated 422 million adults worldwide had DM, with the prevalence almost doubling from 4.7% in 1980 to 8.5% in 2014, the greatest burden of which was in low- and middle-income countries.[5,6] In the Eastern Mediterranean region, the prevalence of DM is particularly high (3.5–30%), with Gulf Cooperation Council countries observed to have some of the highest DM prevalence rates in the region.[7]

Diabetes is associated with several neurological disorders, with stroke being the most well-recognised and, likely, the most common. Diabetes is known to influence almost all varieties of stroke, including large artery stroke due to atherosclerosis, lacunar stroke and, possibly, intracerebral haemorrhage due to microvascular injury and embolic stroke due to diabetes; the latter of which is a significant risk factor for atrial fibrillation and hence part of risk factor assessment.[8] Diabetic individuals have a 2.5–3.6-times higher risk of stroke compared to non-diabetics, with diabetic women at an increased risk compared to men.[5,9–11] Rammal *et al.* estimated the prevalence of diabetes in ischaemic stroke to be 37.5% in the Arab world, based on an analysis of 29 studies of 10,242 patients.[12] In an unpublished case-control study conducted in Oman, the prevalence of DM was 62.3% versus 44.7% among ischaemic stroke cases compared to controls (P <0.001).[13] In another study from Oman based on stroke registry data, 52% of 600 patients with ischaemic stroke had diabetes.[14]

A growing body of literature in recent decades has recognised the link between DM and cerebral atrophy, as well as cognitive dysfunction.[8,15–18] The strong interrelationship between DM and stroke may be due not only to micro- and macrovascular injuries associated with DM, but also to other shared risk factors such as genetic, demographic and lifestyle factors that are likely influenced by age and gender.[8] In terms of the mechanism of vascular injury in diabetes, evidence indicates that hyperglycaemia (and possibly insulin resistance) leads to oxidative stress and the overproduction of reactive oxygen species, triggering multiple biochemical pathways and, ultimately, endothelial dysfunction and vascular injury.[8,15] Early endothelial changes may lead to accelerated macrovascular atherosclerosis as well as changes in microvascular blood flow control and permeability.[16] The phenomenon of 'metabolic memory' complicates the course of DM, with a prolonged progression of micro- and macrovascular complications observed, even after prompt and intensive glycaemic control.[17] Currently, mechanisms of nonvascular brain injury are still being explored. Several of the above mechanisms as well as endothelial dysfunction, alterations in blood brain barrier function and inflammation may contribute to nonvascular neurological injury.[18]

In view of the strong relationship between diabetes and stroke, it is natural to explore various methods of cerebrovascular evaluation to better understand the pathophysiology of these conditions or to predict episodes of cerebrovascular injury. Carotid Doppler ultrasonography is a relatively simple and noninvasive method of visualising the superficial blood vessels and can be used to clinically evaluate the cervical carotid and parts of the vertebral arteries in the context of stroke. Using Doppler ultrasonography, the carotid *intima media* thick-

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ness (CIMT) can be measured and used as surrogate evidence of vascular injury as thickening of the *tunica intima* is known to be a precursor of atherosclerosis.[19,20] The cervical carotid arteries are a fairly easy and convenient location to study this, particularly as they are also the location of the atherosclerotic plaques that lead to stroke. Vascular ultrasonography is another simple method of quantifying the extent of arterial narrowing, as measured by the diameter or cross-sectional area of the *lumen* or by recognising turbulent changes in blood flow.[19,20]

In this issue of *SQUMJ*, Nazish *et al*. have published a retrospective study in which they report a relationship between glycated haemoglobin (HbA1c) and CIMT and carotid plaques among adult ischaemic stroke patients who underwent carotid Doppler ultrasonography in addition to brain imaging.[21] The authors found a significant association between mean HbA1c levels and increased CIMT, but not with the presence of carotid plaques. A regression analysis indicated that dyslipidaemia and age were independently correlated with high CIMT, but not with HbA1c levels.[21] The results of this study are similar to those of other studies exploring the role of carotid ultrasound CIMT and plaque findings as surrogate risk factors for stroke in general, as well as among patients with diabetes.[20,22,23] However, the strength of the relationship between CIMT and stroke among diabetic patients has not yet been determined. Increased CIMT has been associated with other factors influencing stroke, such as hypertension, hyperlipidaemia, smoking, obesity, advanced age and genetic factors.[24] In addition, while some studies have demonstrated CIMT to be a risk factor for diabetes, others have demonstrated only an association on univariate analysis and not as an independent risk factor.[23] Nevertheless, community-based studies of vascular changes are of value because they enhance our understanding of the underlying pathophysiological mechanisms of these conditions; in addition, such research may inform future targets of therapy or be used as markers of treatment efficacy.[19,20,25]

Apart from vascular ultrasonography, other methods may be of use when exploring the complex interactions between diabetes and brain dysfunction. As mentioned earlier, diabetes is a risk factor for other mechanisms of brain injury leading to cerebral small vessel disease (CSVD), non-stroke brain atrophy and cognitive dysfunction.[18] With magnetic resonance imaging (MRI), CSVD is now recognised to comprise a spectrum of brain changes including periventricular hyperintensities, lacunar stroke, intracerebral micro- and macrohaemorrhage, enlarged perivascular spaces and cortical siderosis.[26,27] Several studies have demonstrated an association between diabetic retinopathy and lacunar stroke as well as cognitive dysfunction, although the relation between CSVD and diabetic microangiopathy is not yet clear.[26–28] Apart from conventional changes observed in diabetic retinopathy, such as retinal haemorrhage and changes in vascular diameter, novel methods such as optical coherence tomography, retinal vasculature fractal dimension and laser flowmetry are being explored as methods of detecting brain injury.[18,29] Using videocapillaroscopy, microvasculature changes in the nail bed can be quantified and have been utilised to demonstrate a relationship with diabetic microangiopathy; this method could potentially be explored as a surrogate marker for brain injury.[30] Skin autofluorescence, which reflects the accumulation of advanced glycation endproducts in diabetes, has been associated with brain cortical atrophy.[31]

Overall, MRI is a sensitive method of studying structural changes in the brain. A review of studies addressing MRI findings among diabetic subjects indicated that diffuse brain atrophy as well as increased CSVD changes were associated with diabetes; such changes are only explained in part by age and the presence of other adverse vascular risk factors.[32] MRI is also useful in the detection of microstructural brain lesions among diabetic subjects.[32,33] Attempts to link MRI findings of structural brain abnormalities to histology results may, for example, advance our understanding of the role of diabetic microvascular disease in the context of brain injury. While such methods of studying the relation between diabetes and brain injury may help predict neurological dysfunction, a more attractive application would be to monitor novel treatments.

In conclusion, large artery stroke due to accelerated atherosclerosis is only one mechanism of neurological injury associated with diabetes, with several other mechanisms well recognised in relation to diabetes. Cerebrovascular atherosclerosis can be easily explored using vascular Doppler ultrasonography and angiography. However, CSVD as well as nonvascular diabetic encephalopathy are conditions that may also be explored clinically based on other methods such as retinal or skin vascular changes or utilising advanced brain MRI modalities. More studies are necessary to explore the utility of the latter approach in predicting neurobehavioural changes in patients with diabetes, enhancing our understanding of its pathophysiology and developing better methods of managing these conditions.

References

1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. Lancet Glob Health 2013; 1:e259–81. doi: 10.1016/S2214-109X(13)70089-5.

2. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: Findings from the Global Burden of Disease Study 2010. Lancet 2014; 383:245–54. doi: 10.1016/S0140-6736(13)61953-4.

3. El-Hajj M, Salameh P, Rachidi S, Hosseini H. The epidemiology of stroke in the Middle East. Eur Stroke J 2016; 1:180–98. doi: 10.1177/2396987316654338.

4. World Heart Federation. Stroke. From: www.world-heart-federation.org/cardiovascular-health/stroke Accessed: Nov 2018.

5. World Health Organization. Global report on diabetes. From: www.who.int/diabetes/global-report/en/ Accessed: Nov 2018.

6. International Diabetes Federation. Key messages. From: www.diabetesatlas.org/key-messages.html Accessed: Nov 2018.

7. World Health Organization. World health statistics 2015. From: www.who.int/gho/publications/world_health_statistics/2015/en/ Accessed: Nov 2018.

8. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012; 11:261–71. doi: 10.1016/S1474-4422(12)70005-4.

9. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. Neurology 2004; 62:1558–62. doi: 10.1212/01.WNL.0000123252.55688.05.

10. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart disease and stroke statistics: 2016 update - A report from the American Heart Association. Circulation 2016; 133:e38–360. doi: 10.1161/CIR.0000000000000350.

11. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375:2215–22. doi: 10.1016/S0140-6736(10)60484-9.

12. Rammal SA, Almekhlafi MA. Diabetes mellitus and stroke in the Arab world. J Taibah Univ Med Sci 2016; 11:295–300. doi: 10.1016/j.jtumed.2016.05.001.

13. Ganguly SS, Al-Harthi H, Gujjar AR, Kumar S, Al-Hashmi A, Al-Asmi AR. Risk factors for ischemic stroke in an Omani community: A case-control study. Abstract presented at the 5th International Conference on Neurology & Epidemiology, 18–20 November 2015, Griffith University, Gold Coast, Australia.

14. Gujjar A, Ramachandiran N, Al-Asmi A, Ganguly S, Shoaib R, Al-Asmi A. Ischemic stroke outcomes in Oman: Experience of a university hospital based stroke registry. Neurology 2017; 88:6.278.

15. Qiu C, Sigurdsson S, Zhang Q, Jonsdottir MK, Kjartansson O, Eiriksdottir G, et al. Diabetes, markers of brain pathology and cognitive function: The Age, Gene/Environment Susceptibility-Reykjavik Study. Ann Neurol 2014; 75:138–46. doi: 10.1002/ana.24063.

16. Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes 2005; 54:1615–25. doi: 10.2337/diabetes.54.6.1615.

17. Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: The "metabolic memory" - Is more than just tight glucose control necessary to prevent diabetic complications? J Clin Endocrinol Metab 2009; 94:410–15. doi: 10.1210/jc.2008-1824.

18. 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; 8:134–48. doi: 10.1111/jdi.12545.

19. Kasliwal RR, Bansal M, Desai D, Sharma M. Carotid intima-media thickness: Current evidence, practices, and Indian experience. Indian J Endocrinol Metab 2014; 18:13–22. doi: 10.4103/2230-8210.126522.

20. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011): An update on behalf of the advisory board of the 3rd, 4th and 5th Watching the Risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis 2012; 34:290–6. doi: 10.1159/000343145.

21. Nazish S, Zafar A, Shahid R, Albakr A, Alkhamis FA, Aljaafari D, et al. Relationship between glycated haemoglobin and carotid atherosclerotic disease among patients with acute ischaemic stroke. Sultan Qaboos Univ Med J 2018; 18:e311–17. doi: 10.18295/squmj.2018.18.03.008.

22. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999; 340:14–22. doi: 10.1056/NEJM199901073400103.

23. Lee EJ, Kim HJ, Bae JM, Kim JC, Han HJ, Park CS, et al. Relevance of common carotid intima-media thickness and carotid plaque as risk factors for ischemic stroke in patients with type 2 diabetes mellitus. AJNR Am J Neuroradiol 2007; 28:916–19.

24. Touboul PJ, Labreuche J, Vicaut E, Amarenco P; GENIC Investigators. Carotid intima-media thickness, plaques, and Framingham risk score as independent determinants of stroke risk. Stroke 2005; 36:1741–5. doi: 10.1161/01.STR.0000174490.23495.57.

25. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: The METEOR trial. JAMA 2007; 297:1344–53. doi: 10.1001/jama.297.12.1344.

26. Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010; 9:689–701. doi: 10.1016/S1474-4422(10)70104-6.

27. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: A dynamic whole-brain disease. Stroke Vasc Neurol 2016; 1:83–92. doi: 10.1136/svn-2016-000035.

28. Cheung CY, Ikram MK, Klein R, Wong TY. The clinical implications of recent studies on the structure and function of the retinal microvasculature in diabetes. Diabetologia 2015; 58:871–85. doi: 10.1007/s00125-015-3511-1.

29. Grauslund J, Green A, Kawasaki R, Hodgson L, Sjølie AK, Wong TY. Retinal vascular fractals and microvascular and macrovascular complications in type 1 diabetes. Ophthalmology 2010; 117:1400–5. doi: 10.1016/j.ophtha.2009.10.047.

30. Kuryliszyn-Moskal A, Zarzycki W, Dubicki A, Moskal D, Kosztyła-Hojna B, Hryniewicz A. Clinical usefulness of videocapillaroscopy and selected endothelial cell activation markers in people with type 1 diabetes mellitus complicated by microangiopathy. Adv Med Sci 2017; 62:368–73. doi: 10.1016/j.advms.2016.11.007.

31. Moran C, Münch G, Forbes JM, Beare R, Blizzard L, Venn AJ, et al. Type 2 diabetes, skin autofluorescence, and brain atrophy. Diabetes 2015; 64:279–83. doi: 10.2337/db14-0506.

32. Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: What can we learn from MRI? Diabetes 2014; 63:2244–52. doi: 10.2337/db14-0348.

33. van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: A systematic review. Diabetes Care 2006; 29:2539–48. doi: 10.2337/dc06-1637.