Reduced white matter microstructural integrity in prediabetes: Is early glucose dysmetabolism the culprit?

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Diabetes is a key risk factor for various aging-related brain diseases such as stroke[1] and Alzheimer's disease.[2] Through multiple pathways, diabetes can compromise the brain vascular system and cause widespread brain damage,[3] including brain atrophy, white matter hyperintensities, lacunar infarcts,[4] etc. Since early detection and management of diabetes may be beneficial for delaying the progression of related diseases, much attention has recently been given to prediabetes. Prediabetes is a health condition defined by glycemic variables above normal levels but below the diabetes thresholds. It is recognized as a high-risk state for diabetes progression with a conversion rate of 5−10% per year.[5] In 2021, the International Diabetes Federation estimated the prevalence of impaired fasting glucose and impaired glucose tolerance at about 8% and 16% in adults aged between 55−64 years.[6] An extensive survey using all three glycemic tests (fasting blood glucose, glycosylated hemoglobin, and 2 h post-load blood glucose) estimated that the prevalence of prediabetes in China is 39.5% in the 40−59 age group and 45.8% in the ≥60 age group.[7] As prediabetes is the intermediate state between normal glucose metabolism and diabetes, it is reasonable to suspect that brain damage may have already occurred in this condition. Evidence supporting this theory has emerged over the past few years but is still relatively limited.

In a recent issue of *eBioMedicine*, Jing *et al.* published a paper on brain white matter damage in prediabetes and diabetes.[8] Based on the PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events (PRECISE) study, the authors analyzed brain white matter microstructural integrity in 1205 prediabetes, 504 diabetes, and 509 subjects with normal glucose levels. The prediabetes group was further divided into two subgroups: one group with combined impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), the other without combined IFG/IGT. Compared to subjects with normal glucose metabolism, prediabetes with combined IFG/IGT showed decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in widespread brain regions. After controlling age, sex, and vascular risk factors, the number of tracts with altered diffusion metrics reduced significantly. Nonetheless, diffusion metrics correlated with fasting plasma glucose and Hemoglobin A1c independently. In addition, the volume of white matter hyperintensities also increased in the combined IFG/IGT group.

This cross-sectional investigation was performed in a well-sampled, population-based cohort. Due to the cross-sectional nature, we should be careful when relating the brain alterations found among different groups to the specific state, as other past factors leading to that state may be very relevant. Whether prediabetes could accelerate brain white matter degeneration needs to be proved in future longitudinal observations. Notably, there were significant differences in age and vascular factors (e.g., hypertension, heart disease, smoking) among the control, prediabetes, and diabetes groups. The influence of these factors cannot be entirely removed using linear models. Other confounding factors, such as socioeconomic status or genetic predisposition were not addressed in the current study. The authors used two methods for defining prediabetes, but only subjects with combined IFG/IGT showed changes in white matter diffusion parameters. This may indicate that the combined definition is of greater clinical value, and early intervention in prediabetes defined by this criterion could be beneficial. Nonetheless, we still need a better understanding of the specific mechanisms behind these imaging findings to determine treatment targets. Due to the confounding factors mentioned above, it is still unclear whether elevated glucose is the culprit here. As the known effects of modest elevations of blood glucose levels on brain function appear to be relatively weak,[9] future studies should carefully disentangle the influence of various risk factors in prediabetes.

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Declaration of interests

The authors declare no conflict of interest.

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