Albuminuria and cognitive decline

People with type 2 diabetes (T2DM) have a 50-100% increased risk of developing cognitive decline and dementia as compared to people without T2DM. The reasons for this decline are not yet clearly defined but are likely to be multifactorial, including metabolic and degenerative factors and small blood vessel disease. Identification of factors early in the course of cognitive decline could help identify avenues of intervention that may lead to delay of cognitive decline.

A common complication of T2DM is albuminuria, the excretion of excessive protein into the urine due to “leaky” small blood vessels (called microvessels) in that part of the kidney that filters the blood to rid the body of excess fluid, salts, and breakdown products of metabolism. By age 70 years, 30% of people with T2DM have albuminuria.

Using data from the Action to Control Cardiovascular Risk in Diabetes MIND Study (ACCORD MIND) we found that people with T2DM and albuminuria had a 5.8% decline in executive function (the ability to process information rapidly) during 4 years of follow up as compared to a 2.6% decline in participants without albuminuria during the same time period. Importantly participants in this study (with or without albuminuria) had normal Mini Mental State Exam scores at baseline, a global test of cognitive function. It was our hypothesis that the decline in executive function in association with albuminuria reflected microvascular disease in the brain. This hypothesis has a biological basis since the renal and cerebral circulations are low pressure systems that can be adversely impacted by abnormal blood vessel function. These abnormal processes expose the tissue in both organs to high pressures leading to disease. Put differently, the small blood vessels of the kidney offer a “window” into studying the small blood vessels of the brain.

In a follow-up study we sought to identify anatomical correlates for the early decline in executive function with albuminuria. We examined participants in the study who had baseline and follow up cognitive testing plus baseline and follow up brain MRI scans. We assessed the changes in the two MRIs for decline in total brain and grey matter volume, and for increase in abnormal white matter volume (AWMV). The latter is considered to be a marker of brain small vessel disease and is related to cognitive decline. It was our hypothesis that there would be more AWMV in the brain with albuminuria as compared to its absence.

We found that at baseline, participants with albuminuria had more AWMV than participants without albuminuria on unadjusted analysis. This difference was abolished with adjustment for blood pressure, which was higher in participants with albuminuria compared to those without albuminuria. During follow up, participants with albuminuria had a greater increase in new AWMV than participants without albuminuria on unadjusted analysis. This difference was abolished with adjustment for age and systolic blood pressure. There were no significant differences in gray matter volume and total brain volume between participants with or without albuminuria at baseline or during follow-up. In other words, we did not find unique anatomical brain abnormalities associated with albuminuria that explained the decline in early cognitive decline. Rather the effects

of albuminuria on cognitive function appeared to be mediated by hypertension and older age.

Given the lack of specific brain findings in association with albuminuria we are now extending our studies to examine a panel of biomarkers that include inflammatory factors and blood vessel function factors to see which ones associate with albuminuria and cognitive decline. We believe that the findings will yield important information regarding microvascular disease and the development of early cognitive decline in T2DM.

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