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Recognizing the risks of type 2 diabetes for the brain

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It is well known that type 2 diabetes compromises the health and function of multiple organs, including the kidneys, eyes and heart. What some physician assistants may not realize is that convincing evidence has accumulated over the past few years that an important relationship between diabetes and brain function exists. For example, type 2 diabetes increases the likelihood that a person will develop dementia (Ott, et al., 1999), including Alzheimer's disease and vascular dementia. Type 2 diabetes can also accelerate mild cognitive decline comparable to effects seen with aging, such as slower processing speeds (see (Reijmer, et al., 2010) for review). At present, there is no “smoking gun” linking cognitive decline to diabetes. However, current science offers two strong lines of evidence that might explain the connection, one pointing to insulin sensitivity and the other to cardiovascular disease.

We now understand that insulin plays an important role both in regulating brain glucose and in signaling processes within the brain. In fact, the links between insulin regulation and cognition are so strong that some have suggested that Alzheimer's disease might be best described as “type 3 diabetes” (see (de la Monte and Wands, 2008) for review). Regions affected by Alzheimer's disease are especially rich in insulin receptors (see (Cholerton, Baker and Craft, 2011, Schioth, et al., 2012)). Human research shows that dementia incidence is associated with a low insulin response to a glucose challenge, high fasting plasma glucose (FPG), and 2-hour fasting glucose after oral glucose tolerance test (Ronnemaa, et al., 2008, Ronnemaa, et al., 2009). In addition, impaired insulin sensitivity is linked with atrophy of the temporal lobe and cognitive performance (Benedict, et al., 2012). Interestingly, evidence is emerging that administration of intranasal insulin, which delivers insulin preferentially to the brain, is associated with improved memory performance in younger adults and persons with early Alzheimer's disease (Schioth, et al., 2012).

However, the role type 2 diabetes plays in significantly increases risk for cardiovascular disease, including atherosclerosis, hypertension, heart failure, stroke, and myocardial infarction, should not be discounted. Cardiovascular disease increases the risk for dementia and milder cognitive impairments independent of diabetes (for review see (DeCarli, 2013)). Hypertension is illustrative of this link. Hypertension is a common comorbidity of type 2 diabetes that is associated with atrophy of overall grey matter, hippocampus, and frontal cortex (Raz, et al., 2005, Raz, Rodrigue, Kennedy and Acker, 2007). Hypertension is also strongly associated with leukoairiosis (Raz, Rodrigue, Kennedy and Acker, 2007), a disease of white matter in the brain that is common in aging and associated with slower processing speed (Arntzen, Schirmer, Wilsgaard and Mathiesen, 2011). In a postmortem study in

humans with Alzheimer's disease, researchers found that while patients with diabetes had a comparable level of Alzheimer's pathology to those without diabetes, the patients with diabetes were more likely to experience cerebral infarctions (Arvanitakis, et al., 2006). In short, the risk for clinically diagnosed cardiovascular disease imparted by type 2 diabetes almost assuredly raises the risk for cognitive decline in this group of people.

My colleagues and I recently completed an analysis looking to see if evidence of subclinical cardiovascular disease raised the risk of poorer cognitive function a few years later. In our study, subclinical cardiovascular disease was defined as coronary calcification measured using computed tomography. Part of what made this study unique was the fact that we included a measure of subclinical CVD rather than reported CVD events. Also, the population was unique. We studied a group of aging siblings in which about 80% had type 2 diabetes. Why is this population important to study? First, because they share some genetic and environmental background, it is less likely that these factors explain any observed differences between those with and without diabetes. Second, the siblings without diabetes were not healthy controls, as are most commonly used. Some of our patients also had evidence of subclinical CVD, were overweight, or had insulin resistance. Often, comparisons use controls who are largely free of any chronic disease. While this helps isolate the effects of the disease, people who age disease-free are a minority, sometimes called “super-agers”. The sibling comparison group is in many ways a more representative comparison group than “super-agers”.

Several observations we made could be important for physician assistants. First, the presence of diabetes was associated with poorer cognitive performance in processing speed, verbal memory, and executive function. That is, patients with diabetes tended to have poorer cognitive performance, even when compared with siblings with similar genetic background and environmental exposures. What role did cardiovascular disease play in this? Adjusting for subclinical cardiovascular disease reduced the association between cognition and diabetes to non-significance and was predictive of lower cognitive performance. Put another way, the variation in subclinical CVD was a more powerful predictor of lower cognitive performance than the presence of diabetes. Interestingly, subclinical CVD also predicted lower cognitive performance in those patients without diabetes.

As a neuroscientist, as yet unexplained nuances of exactly how the brain is affected by a metabolic disturbance in the body are my primary focus. My clinical colleagues and I believe that even in the absence of a clear causal pathway, what we know now about the subclinical risks of type 2 diabetes for the brain can begin to inform clinical practice. It is important to note that the magnitude of the effect of both diabetes and CVD on cognition was relatively small; almost everyone in the study was above the cutoff for dementia on the Mini-Mental State Examination. Even though these relatively small effects might not be clinically evident, subtle cognitive changes in executive function, verbal memory, and processing speed could affect patients' ability to comprehend and follow-through on the complex medical regimens often necessitated by diabetes. Knowing that patients with risk factors for CVD or diabetes might have slower processing speed, clinicians could slow down speech. If the ability to repeat back what was said to you a few minutes earlier might be impaired, it is sensible to ask patients to repeat information back to you (“teach back”

techniques) or provide information in writing. Importantly, some patients who will benefit from these modest accommodations might not present with any overt disease. Finally, understanding that diseases of the body, like diabetes and CVD, also pose a risk to the brain may motivate patients to embrace healthy lifestyle changes.

These results reinforce the idea that disease processes can affect function before they are clinically recognizable. The next time you encounter someone who has risk factors for diabetes, such as borderline hypertension or borderline elevated blood sugars, keep in mind that these subclinical changes may already be influencing your patient's ability to understand and follow through on the important health care instructions you give them. The information we are learning about subclinical disease gives both providers and patients an impetus to be proactive and make change in communication and lifestyle before disease is actually present.

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