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Editorial

Diabetes and the brain: More information needed

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Hyperglycemia is clearly associated with the long-term risk of diabetes-related microvascular and macrovascular complications. Treatment to reduce hyperglycemia, as determined by hemoglobin A1c (HbA1c), reduces the occurrence and slows the progression of retinopathy, nephropathy, and neuropathy in adults [1] and adolescents [2,3] as well as the macrovascular complications [4]. Despite overall improved glycemic control from newer diabetes management technologies that have developed during the last three decades (insulin analogs, self-blood glucose monitoring, insulin pumps, and continuous glucose monitoring [CGM] sensors), hypoglycemia continues to be a limiting factor in achieving a euglycemic state in insulin-treated (type 1 and insulin-requiring type 2) diabetes mellitus [5]. Even today, with the best of technologies available, persons with type 1 diabetes mellitus (T1DM) spend a significant portion of each day hyperglycemic and/or hypoglycemic. This is clear from many studies, most notably from the JDRF CGM Study [6] in which an average of 395 min (6.5 hr) of the day were spent with blood glucoses (BG) >180 mg/dL, 101 min (1.7 hr) with BG >250 mg/dL and 60 min (1 hr) of the day with BGs <70 mg/dL for adults using CGM. Hence, even under the best of circumstances and using the most up-to-date technology under the guidance of some of the most experienced diabetes practitioners available, most diabetic subjects are either hypo- or hyperglycemic for about one-third of their lives.

This situation is even more problematic in children. In the same JDRF CGM Study [6], for the subjects 8 to 14 years old using CGM, 635 min (10.6 hr) of the day were spent with BGs >180 mg/dL, 268 min (4.5 hr) with BG >250 mg/dL and 47 min (0.8 hr) with BG <70 mg/dL. Nearly half the day, on average, was spent either hypo- or hyperglycemic. In years past, when hypoglycemia was considered to be the major contributor to cognitive deficits in children with diabetes, we were satisfied with allowing a higher glycemic target in children so as to avoid hypoglycemia. Coupling the observations from the JDRF CGM study with the associated cognitive impairment in either hypoglycemic or hyperglycemic state leaves caregivers of patients with T1DM with an important challenge: What is the best range to target blood glucose to maximize the benefits of glycemic control for the prevention of the long-term vascular complications while minimizing the potential for cognitive and CNS complications associated with both hypoglycemia and hyperglycemia?

In this issue of the *Journal of Pediatric Neuroradiology*, Kaufmann et al. report their findings from a cross-sectional study using cognitive testing and brain MRI in 30 "pediatric patients" (6 - 20 years old) with T1DM and 19 similarly-aged non-diabetic controls. The T1DM subjects were analyzed in two groups, one (n = 15) with HbA1c < 8.0% ("low HbA1c group") and the other with

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HbA1c ≥ 8.0% (n = 15; "high HbA1c group"). It should be noted that there were a similar number (about 1/3) of subjects with severe hypoglycemia in the two groups. Differences in spatial working memory (SWM) favoring the controls were found between the non-diabetic controls and the diabetic subjects. However, differences in SWM between the "high HbA1c" and the "low HbA1c" groups were not significant. For the brain structure as assessed by MRI, T1DM subjects differed from controls in the total gray matter volume with gray matter differences (favoring controls) in the left anterior cingulate and left cuneus, and white matter differences (again favoring controls) in the temporal lobes bilaterally and the left middle occipital gyrus. Comparing the "high HbA1c" to the "low HbA1c" groups, the "high HbA1c" group had less gray matter in the right parietal region, less white matter bilaterally in the frontal regions, and larger gray matter volume in the middle temporal gyrus. Although the present study did not show differences in cognitive function between the "high" and "low" HbA1c groups, there was a strong correlation (r = 0.57, p = 0.001) between the error rate on the SWM task and the white matter structure in the left uncus. The authors state, and I believe they are correct, that these findings are among the first to report experimental evidence linking specific brain structural changes with specific cognitive alterations in children with T1DM. This has not so far been addressed by prior studies [7–13], and represents an important step toward better understanding of the risks of diabetes on brain function and structure.

The functional and structural differences reported by Kaufmann et al. [14] mimic those previously reported by our group (Hershey; Perantie; *et al*; [7–9]) from St. Louis, Missouri, USA and the group from Australia (Northam; Lin; *et al*; [10–13]). However, these investigators have not reported associations between differences in structural and functional domains, as was done by Kaufmann et al. [14]. If these associations are confirmed and expanded upon in future studies, it would provide important information about the potential etiology and pathophysiology of cognitive deficits and structural changes of the brain associated with diabetes.

It is important to note that in this report by Kaufmann et al. [14] little attempt was made to distinguish the effects of hypoglycemia from those of hyperglycemia. In the results from the St. Louis group, the cognitive and structural domains affected by hypoglycemia differed from those affected by hyperglycemia. For the cognitive domains, severe hypoglycemia was associated with lower spatial intelligence quotient (IQ) (p = 0.02) and worse spatial memory (p = 0.04); these findings were most pronounced for those with a history of multiple severe hypoglycemic events before the age of five years. Hyperglycemia, however, was associated with lower verbal/general IQ (p = 0.02) but not significantly with spatial IQ or spatial memory [8]. For the structural domains, hypoglycemia was associated with reduced gray matter volume in the left superior temporal/occipital cortex [8] and increased volume of the hippocampus [9], whereas hyperglycemia was associated with reduced gray matter in the precuneus (bilateral) and decreased white matter in the right parietal region [8]. These data strongly suggest that hypoglycemia and hyperglycemia are differentially related to both cognitive skills and brain structure.

Our data [7] and that of the Australian group [10,11] suggest that those with earlier onset of T1DM and especially those with severe hypoglycemia at a young age may be more at risk for cognitive deficits associated with T1DM. In the current manuscript, using multiple regression analysis, diabetes duration, age at onset and white matter volume in the uncus explained 56% of the variance in cognitive performance, whereas HbA1c level, intelligence, and gray and white matter volumes in whole brain and regions of interest (other than the uncus) did not improve the model.

These data add to the now growing knowledge base indicating that both hypoglycemia and hyperglycemia are associated with long-term deficits in cognitive function and structural brain alterations. However, the nature and magnitude of these alterations and the other risk factors that contribute to them are less clear. What mechanisms play a role in these alterations? What neural networks and pathways are involved? The studies performed to date are largely descriptive, cross-sectional and hypothesis-generating. Specific hypothesis-testing studies are needed. With the emerging advances in neuroimaging techniques, and an increasing ability to study subjects at different ages, developmental stages and duration of diabetes in longitudinal studies, we can begin to address many of the remaining unanswered questions about the relationship and mechanisms underlying the effects of diabetes, hypoglycemia and hyperglycemia on cognitive function and brain structure.

Ultimately, the goal must be to diminish to comorbidities and complications related to diabetes mellitus and its treatment. One approach would be to develop better methods of physiologic insulin replacement to optimize glycemic control and minimize both hyper- and hypoglycemia. To accomplish this goal, diabetologists must continue to strive for better technologies to

optimize insulin therapy and minimize glucose variability. Approaches might include developing improved insulin analogs, utilization of other medications or hormones, better continuous glucose monitoring (CGM) systems, a "closed-loop" insulin delivery system or "artificial pancreas", and safe and effective approaches to ß-cell preservation or replacement.

A second approach to minimize the complications and comorbidities related to diabetes mellitus and its treatment would be to develop approaches to safely mitigate the effects of hyper- and hypoglycemia on tissues and organs. Future exploration in neuroscience and neuroimaging may provide a better understanding of how glucose (high or low) affects brain structure and function, which could lead to the development of strategies to reduce these comorbidities.

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