Response to Does the Improvement in Insulin Sensitivity Mediate the Beneficial Effects of Weight Loss on Cognitive Function?

We thank Stephan and Siervo for their suggestion that we examine glucose and insulin levels as potential mediators of the relationship between lifestyle modifications and improved neurocognition in the Exercise and Nutritional Interventions for Cardiovascular Health Study. Observational studies have reported that impaired insulin resistance and glucose metabolism are associated with deficits in neurocognitive functioning, and there is preliminary evidence from interventional studies that improved neurocognition associated with lifestyle modifications may be mediated by improved glucoregulation. For example, Baker et al demonstrated that aerobic exercise improved executive control processes, with effects more pronounced for women compared with men. Because women also showed greater improvements in glucose metabolism and insulin sensitivity, it was suggested that neurocognitive improvements may be mediated by cardiovascular and metabolic effects of exercise. In addition, 2 recent dietary intervention studies cited by Stephan and Siervo also provide support for the role of improved insulin levels on neurocognition. In the study by Brinkworth et al, both a very low carbohydrate diet and a low-fat diet achieved similar reductions in weight and improved glucose metabolism, along with improvements in cognitive functioning; furthermore, changes in Digit Span performance were inversely correlated with fasting insulin levels. Witte et al did not observe treatment group differences in Digit Span or Trail Making test performance, but caloric restriction was associated with improved performance on the Rey Auditory Verbal Learning Task, and decreases in fasting insulin were correlated with improved Rey Auditory Verbal Learning Task performance among a subset of patients who lost the most weight, although formal test of mediation was not performed.

In the Exercise and Nutritional Interventions for Cardiovascular Health Study, patients randomized to the Dietary Approaches to Stop Hypertension (DASH) diet combined with a behavioral weight management program lost more weight and exhibited greater improvements in insulin sensitivity and glucose response compared with a usual diet/exercise control condition (UC), whereas those patients receiving the DASH diet alone were not different from the UC. This finding was confirmed in the present analysis despite the reduced sample size. However, neither insulin sensitivity nor glucose response was related to neuropsychological outcomes: changes in psychomotor speed were not related to changes in insulin sensitivity or to changes in glucose response (P = 0.404 and P = 0.571, respectively). Similarly, changes in executive function also were unrelated to changes in insulin sensitivity and glucose response (P = 0.937 and P = 0.872, respectively). Not surprisingly, formal tests for mediation (indirect effects) were not statistically significant for insulin sensitivity and psychomotor speed (DASH diet combined with a behavioral weight management program versus UC, P = 0.982; DASH diet alone versus UC, P = 0.982) or executive function (DASH diet combined with a behavioral weight management program versus UC, P = 0.452; DASH diet alone versus UC, P = 0.525). We observed a similar pattern for the tests of glucose response as a mediator. Thus, despite improvements in neurocognitive performance and insulin and glucose responses in patients receiving the DASH diet combined with a behavioral weight management program, we did not find evidence for a mediating role of glucose metabolism or insulin sensitivity on neurocognitive performance. We conclude that, although improvements in glucoregulation may be a plausible mechanism to explain lifestyle-related improvements in neurocognition, data from the Exercise and Nutritional Interventions for Cardiovascular Health Trial do not support this relationship.

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Disclosures

None.

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