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

To the Editor:

Smith et al.\(^1\) have recently published an article reporting the beneficial effects of intentional weight loss achieved by a combination of dietary behavioral modification and aerobic exercise on cognitive function in hypertensive obese subjects. The randomized study design, the comprehensive assessment of cognitive function across multiple domains, and the controlled dietary and physical activity interventions were the main features of the article. The mechanistic link between changes in metabolic function after weight loss and cognitive improvement was, however, not explored despite metabolic findings on changes in body composition and plasma lipid, insulin, and glucose levels being reported in a separate article published from the same study in this journal.\(^2\)

Although we recognize the pragmatic necessity of reporting the cognitive and metabolic findings in 2 different articles, we note the missed opportunity to integrate the analysis of changes in cognition associated with weight loss with the metabolic findings. This analysis would have provided a unique opportunity to explore the mechanistic link between weight loss and cognitive improvement. This is necessary to shed light on the causal association between dietary restriction and reduced risk of neurodegenerative disorders observed in experimental animal models and epidemiological analyses.\(^3\) Possible mechanisms have been preliminarily explored in 2 recent human studies investigating the effects of weight loss on cognition.\(^4,5\) The first, a 1-year randomized clinical trial in 106 overweight and obese subjects, showed an inverse correlation ($r = -0.34; P = 0.007$) between changes in fasting insulin levels after weight loss with changes in working memory performance assessed using the digit span backward test.\(^4\) The weight loss achieved after 12 months was significant ($13.7 \pm 1.8$ kg), and insulin levels decreased by 40%. These results were replicated in a sample of 30 elderly overweight and obese subjects after a smaller but significant weight loss of 2.4 kg after a 3-month intervention with a 30% caloric restriction. An inverse correlation ($r = -0.81; P = 0.014$) between fasting insulin levels and changes in memory scores assessed by the Rey Auditory Verbal Learning Task was observed in a subsample (9 subjects).\(^5\)

The replication of the same finding in 2 different studies with varying study design, samples, and weight loss interventions supports the biological plausibility of the mechanistic link between improvements in insulin sensitivity and memory function in overweight and obese subjects. The metabolic and neuropsychological mechanisms underpinning these changes remain to be elucidated, but possible hypotheses include the following: (1) an improvement in glucose use by neuronal cells; (2) better regulation of cerebral flood flow; (3) increase in leptin sensitivity; or (4) a more efficient degradation of $\beta$-amyloid by the insulin degrading enzyme.

Additional analyses by Smith et al.\(^1\) investigating the associations between changes in cognitive function with modifications in insulin sensitivity, glucose, and lipids would provide a unique opportunity to corroborate and extend existing but still unproven hypotheses of a metabolic effect on cognitive improvement after weight loss. A better understanding of the causal pathways would help to plan more cost-effective measures for the prevention of cognitive decline in at-risk individuals who may benefit from weight loss interventions.

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