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Insulin Resistance and Cognitive Decline May Be Common Soil for Frailty Syndrome

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In the April, 2007, issue of the *Archives*, Barzilay et al¹ reported that 2 components of the metabolic syndrome, insulin resistance (IR) and inflammation, are associated with the risk of frailty in older persons without diabetes mellitus, severe cognitive impairment, or other chronic illnesses. Using the homeostasis model of assessment (HOMA), they found that IR and C-reactive protein were consistently associated with an increased risk of developing frailty, even after adjusting for confounders. The authors propose that there is a causative relationship between IR and frailty. Specifically, they propose that the progressive age-associated decline of insulin sensitivity causes an imbalance toward catabolism, which is clinically expressed as an accelerated decline of muscle mass and strength. Such findings further substantiate previous findings from the “Invecchiare in Chianti” (InCHIANTI) study showing that IR-HOMA score was independently associated with poor muscle strength in older persons.² Barzilay et al¹ also hypothesized the existence of an inflammatory IR pathway that could contribute to muscle weakness and poor physical performance. An independent cross-sectional relationship between inflammatory markers and IR-HOMA score was previously suggested from analyses performed in the InCHIANTI database that underlined significant associations among IR and diverse inflammatory cytokines.³ Interestingly, Barzilay et al¹ did not consider cognitive decline as part of their outcome. Indeed, cognitive impairment is often observed in frail older persons, and several authors have proposed that cognitive impairment should be an essential component of the frailty definition.⁴

There is strong evidence showing that normal functioning of the insulin-signaling pathway is crucial for the maintenance of adequate cognitive function.⁵ We studied the relationship between IR-HOMA score and global cognitive performance (Mini-Mental State Examination [MMSE]) as well as executive functioning (Trail-Making Test [TMT] times) in 597 older persons with a mean age of 73 years from the InCHIANTI study.⁵ After adjusting for multiple confounders including MMSE score, IR-HOMA score was significantly associated with poor visual scanning (TMT-A) ($\beta=11.005$; $P=.02$), poor visual scanning with added cognitive flexibility (TMT-B) ($\beta=28.379$; $P<.001$), and poor cognitive efficiency (difference between TMT-B and TMT-A) ($\beta=17.374$; $P=.01$).⁵

These data support the notion that insulin modulates glucose use in the central nervous system through receptors located in the hippocampus and frontal cortex (which is putatively associated with executive functioning). Given our findings^{2,3,5} and those of Barzilay et al,¹ it would be interesting to verify if cognitive decline is associated with increased risk of developing frailty in older nondemented persons and whether such correlation is mediated by IR.

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