

Commentary

The Association Between Insulin Resistance, Depression, and Dementia

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Drs. Rasgon and Jarvik argue that insulin resistance may be linked to affective and cognitive disorders (1). Rather than taking position on this intriguing hypothesis, we wish

to review the epidemiological data on the association between insulin resistance and diabetes, depression, and Alzheimer's disease (AD).

Insulin Resistance: What Is It?

In a pathophysiological sense, insulin resistance can simply be defined as any state where the insulin dose–response curve is shifted to the right. However, in a clinical sense, insulin resistance is best known in the context of type 2 diabetes and prediabetes and is usually associated with obesity. Type 2 diabetes is the outcome of a long, slow process where initial insulin resistance, due to a mix of genetic predisposition and behavioral factors, worsens to glucose intolerance and ultimately overt diabetes (i.e., hyperglycemia). Thus, “insulin resistance” as a clinical concept has no clear boundaries. It is, however, accompanied by a vast array of abnormalities that include obesity, hypertension, dyslipidemia, hyperleptinemia, and a hypercoagulable state. These symptoms are nowadays recognized as the “metabolic syndrome” (2), which implies a high risk for cardiovascular disease even in the absence of overt hyperglycemia (3).

Two important remarks should be made in connection with the above considerations: 1) Given the impressive prevalence of insulin resistance as established by several studies (4,5) and the lack of recognized diagnostic criteria, a control group truly free of insulin resistance is difficult to identify for studies on metabolic, cardiovascular, or psychiatric outcomes. 2) The interpretation of these types of studies needs to take into account duration, coexistent metabolic abnormalities, and the presence of diabetes (i.e., the contribution of insulin resistance per se versus hyperglycemia).

Insulin Resistance and Depression

A link between diabetes and depression has long been suspected. However, the prevalence of depression in diabetes or insulin-resistant state is hard to quantify. In a recent systematic review, the risk of depression is doubled by diabetes, a remarkably consistent figure across studies (6).

A possible explanation would be a common genetic background accounting for both diabetes and depression. Alternatively, depression as a “stress situation” could worsen preexisting insulin resistance and, for example, convert prediabetes to overt diabetes. The psychological stress response hypothesis is not only restricted to depression. A major Dutch population study found a correlation between the number of stressful life situations and the incidence of diabetes (7). One explanation is simply that these stressful situations would bring the patient more frequently to the doctor's attention, and give him more opportunity to screen for diabetes. However, this relationship was still present when diabetes detected by systematic screening of the whole population (including newly discovered cases rather than only self-reported diabetes) was considered (7).

Whether depression is more frequent with diabetes than with any other chronic disease is very difficult to demonstrate convincingly. Actually, the similar rates of depression in type 1 and type 2 diabetes argue against a major role of insulin resistance per se (6).

Diabetes and AD

The association between diabetes or insulin resistance and AD is rather complex and many issues still remain unsolved.

An epidemiological study in search of midlife risk factors associated with AD has identified the apolipoprotein E-4 (APOE-4) genotype, arterial hypertension, and hypercholesterolemia (8). Although the latter two are features of the metabolic syndrome, diabetes was not identified as a risk factor in this study. In an older population, the Rotterdam study found an association between diabetes and dementia that was stronger for vascular dementia than for AD (9). In the cross-sectional Kuopio study, impaired glucose tolerance was found to confer an approximately twofold increase in the risk for AD; this relationship was strengthened by the exclusion of APOE e4 carriers (10). Also, in the prospective Honolulu-Asia Aging Study, a significant increase in the incidence of dementia in diabetic patients was found over 3 to 4 years, but the association was once again stronger for vascular dementia than for AD (11). Importantly, the association between diabetes and AD was lost when only incident cases of diabetes or diabetes diagnosed by an elevated postchallenge glucose level (blood sugar >11 mmol/l during an oral glucose tolerance test) were considered. Thus, dementia is more clearly associated with established diabetes, pointing to a role for hyperglycemia rather than for insulin resistance per se.

How should we then evaluate the observations that point towards an association between insulin resistance and AD? Craft and colleagues (12) have reported reduced insulin sensitivity in AD patients. This finding was limited to patients negative for the APOE-4 genotype and to female patients with mild insulin resistance that did not represent the full metabolic syndrome (normal fasting blood sugar, no obesity). In the Kuopio study, impaired glucose tolerance was associated with a small decline in the Mini-Mental State Exam and with a low magnitude decrease of long-term verbal memory (13). These results provide an association between insulin resistance and cognitive function but fail to demonstrate a direct causative effect on AD. However, if as suggested by several studies, mild insulin resistance was causal in the pathogenesis of cognitive decline and AD, the remaining question is “Why is the association between more severe forms of insulin resistance and AD so difficult to demonstrate?”

The importance of insulin signalling in the brain has been firmly established in several animal studies. One intriguing finding is the role of the central nervous system in food intake and obesity. Intracerebroventricular injection of insulin in monkeys induces reduced food intake and resulted in significant weight loss (14). Conversely, selective inactivation of the central nervous system insulin receptor in mice (by tissue-specific gene knock-out) caused increased food intake, obesity, and insulin resistance (15). Thus, dysfunction of brain insulin receptors, possibly induced by the pathological process underlying AD, can induce peripheral insulin resistance. Once again, these observations suggest that insulin resistance in AD is of secondary low magnitude and quite distinct from the insulin resistance/metabolic syndrome that underlies type 2 diabetes.

Conclusions and Clinical Implications

The metabolic syndrome and diabetes are associated with both depression and dementia. However, diabetes is a much

stronger risk factor for vascular dementia than for AD. The insulin resistance associated with AD is most likely secondary rather than causal, of low severity, and distinct from the metabolic syndrome. Whether therapeutic interventions targeted at long-term correction of insulin resistance can improve functional status in AD patients remains to be demonstrated.

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