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MINI-REVIEW

Optimizing clinical phenotyping to better delineate the complex relationship between type 2 diabetes and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia, and its prevalence is increasing rapidly. According to the Alzheimer's Association, over 5 million adults in the United States over the age of 65 years currently have AD, and this number is expected to exceed 13 million by 2050 in the absence of novel, preventative strategies. Epidemiologic studies have implicated the presence of type 2 diabetes mellitus (T2DM) specifically at midlife as a key modifiable risk factor for AD, and AD may increase risk of dysglycemia and T2DM. However, data have been inconsistent with regard to the magnitude of AD risk attributable to T2DM, and the pathways underlying this apparent relationship remain poorly understood. Elucidating the impact of T2DM on AD risk and progression requires greater attention to the myriad facets of T2DM pathophysiology, its comorbid conditions, and attendant treatment modalities, all of which may differentially impact the relationships among T2DM, cognitive decline, and AD. This mini-review will summarize the discrete facets of T2DM that may influence AD risk and highlight the importance of careful clinical phenotyping in both epidemiologic and interventional studies to better delineate the key pathways and mechanisms linking T2DM and AD.

INTRODUCTION

Alzheimer's Disease (AD) is rising rapidly on a global scale, with a prevalence that is anticipated to triple between 2010 and 2050.[1] The 3 strongest risk factors for late-onset AD are advanced age, female sex, and presence of the apolipoprotein E ε4 allele (APOE4),[2] but many modifiable risk factors also have been identified. Remarkably, modifiable risk factors may account for up to half of all AD cases,[1] underscoring the critical importance of identifying areas of intervention that promise the greatest reduction in AD incidence.

In addition to its histopathologic hallmarks of extracellular amyloid beta (Aβ) deposition and intracellular tau neurofibrillary tangles, AD is characterized by metabolic alterations, including central insulin resistance, reduced glucose metabolism, and mitochondrial dysfunction.[3,4] These metabolic changes arise early in AD evolution and are evident in both the prodromal phase of mild cognitive impairment (MCI) and asymptomatic individuals with elevated genetic risk of AD.[5] In part because of these early, pathogenic changes in energy metabolism, epidemiologic studies have examined type 2 diabetes mellitus (T2DM) as a potential modifiable risk factor for AD. Although larger studies generally have found a positive association between T2DM and AD risk, these studies have been not been consistent with regard to the magnitude of AD risk imparted

by T2DM.[6] In parallel with these inconsistencies, the key mechanisms underlying the apparent association between T2DM and AD remain incompletely understood. Whereas some of the prior, conflicting findings have been ascribed to methodologic differences among studies, these variable results also may reflect the complexity and phenotypic heterogeneity of T2DM.

Individuals with T2DM display varying degrees of insulin resistance, adiposity, and glycemic control, and T2DM variably clusters with comorbid conditions, including hypertension, dyslipidemia, and depression. This mini-review will summarize the literature to date regarding links between AD risk and these myriad facets of T2DM phenotype (Figure 1). Further, it will highlight the need for thorough clinical phenotyping of patients with T2DM in clinical studies to identify the aspects of T2DM-associated pathology, treatment, and comorbidities that most strongly influence AD risk. Notably, the scope of this mini-review is limited to T2DM, as the relationship between type 1 diabetes and cognitive dysfunction is distinct and the subject of a recent comprehensive review.[7] Better delineating the relationships among these numerous facets of T2DM phenotype and AD could enhance understanding of the specific pathogenic mechanisms underlying AD risk and generate targeted intervention strategies that best address these implicated pathways.

FIGURE 1 Numerous facets of type 2 diabetes pathology (blue circles) could augment Alzheimer's disease risk, whereas interventions (green circles) could mitigate risk

FACETS OF T2DM PHENOTYPE

Insulin resistance

Peripheral insulin resistance has been invoked as a key facet of T2DM that increases AD risk. Insulin is also found in the brain and, although it is not required for brain glucose uptake, evidence of brain insulin resistance has been found in AD, including reduced insulin and insulin-like growth factor-1 (IGF-1) signaling.[5] Several states of metabolic dysregulation, including obesity and hypertriglyceridemia, have been shown to affect brain insulin transport and signaling.[8] Furthermore, animal studies have suggested that peripheral insulin resistance can exacerbate both central insulin resistance and AD pathology.[4] Brain endothelial cells transport circulating insulin into the central nervous system through tightly regulated transcytosis, and insulin also signals within these cells and thereby contributes to blood-barrier integrity.[9] Central insulin plays critical roles in neuroprotection, learning, and memory, as well as energy balance and reproduction.[9] Insulin also plays several putative protective functions specific to AD pathogenesis, including reducing the number of neuronal Aβ binding sites, inhibiting Aβ deposition, and inhibiting tau phosphorylation and accumulation.[4]

Insulin and Aβ are both substrates for insulin-degrading enzyme (IDE) and induce IDE activity (Figure 2). Insulin can promote Aβ degradation and thereby inhibit its deposition through induction of IDE activity, but hyperinsulinemia can lead to reduced Aβ degradation via competition for IDE.[6] Conversely, Aβ can induce IDE activity and therefore lead to increased degradation of insulin in regions of the brain specifically implicated in memory and AD, including cortex and hippocampus.[9] Thus, either insulin excess or diminished insulin signaling can promote Aβ deposition in the brain. Insulin resistance, a state that entails variable degrees of hyperinsulinemia and deficient insulin signaling, therefore could contribute to several pathogenic facets of AD, including compromise of blood-barrier integrity, loss of neuronal protection, and reduced inhibition of Aβ and phospho-tau deposition.

Importantly, peripheral and central insulin resistance can be uncoupled,[4] underscoring that the regulation and biological roles of insulin in the brain and periphery are distinct. Peripheral insulin resistance in T2DM is specific to the glucoregulatory effects of insulin signaling but not its lipogenic or mitogenic effects, and central insulin signaling plays glucoregulatory roles only in limited regions and cell types in the brain.[10,11] Insulin concentrations and signaling also are differentially regulated in the periphery and the brain. The source and regulation of brain insulin levels is an area of active study; most evidence supports transport across the blood-brain barrier supplying the bulk of brain insulin with potential insulin production in certain brain

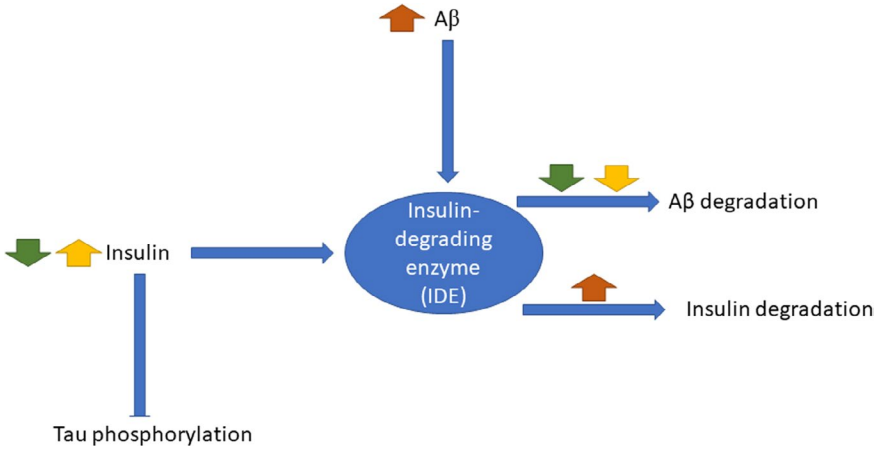

FIGURE 2 Regulation of amyloid beta (Aβ) degradation and tau phosphorylation requires adequate but not excessive insulin concentrations in brain. Inadequate insulin (green arrows) fails to induce Aβ degradation by insulin-degrading enzyme (IDE), but excessively high insulin concentrations (yellow arrows) compete with Aβ as substrate for IDE and promote Aβ deposition. Insulin signaling also inhibits tau phosphorylation via regulation of glycogen synthase kinase-3β activity. Finally, increased Aβ (orange arrows) can lead to accelerated insulin degradation through induction of IDE activity[6,9]

regions.[9] Insulin exposure in the brain is also regulated in a highly region-specific fashion, as glucose ingestion increases insulin concentrations in the hypothalamus but not in other brain regions.[11] Regulation of insulin receptors may also differ for the periphery and the brain; thus, elevated circulating insulin downregulates insulin receptors in the periphery, but this stimulus does not appear to decrease brain insulin receptor level or function.[9]

Nonetheless, although insulin resistance is commonly viewed as a hallmark of T2DM, peripheral insulin resistance is highly prevalent among individuals who are overweight and obese but without T2DM, and progressive pancreatic β-cell loss, rather than progressive insulin resistance, is believed to underlie the transition to overt T2DM.[10] Stratifying individuals by severity of insulin resistance therefore is essential in future work to better understand the magnitude of AD risk conferred specifically by this facet of T2DM. These aggregate observations also support the need for greater understanding of both cell type- and region-specific changes in central insulin signaling that may arise in T2DM and of the relationship between peripheral and central insulin signaling. Such understanding not only is needed for delineating the mechanistic links between T2DM and AD but, critically, would facilitate more precise characterization of the specific molecular changes currently grouped broadly as "insulin resistance."

Hyperglycemia

Hyperglycemia has been shown to predict increased risk of dementia in individuals with and without T2DM.[12] Limited autopsy data suggest that hyperglycemia may promote AD pathology, as postmortem brain analyses demonstrated greater Aβ plaque burden, tau-positive cells, and microglial activation in patients with both AD and T2DM than in those with AD alone.[6] Further, these findings were observed in association with higher levels of advanced glycation end-products (AGEs) and cells expressing the receptor for AGEs, suggesting a link between glucose-mediated stress and the hallmark pathologic features of AD. In an animal model utilizing the toxic glucose analog alloxan to induce pancreatic β-cell loss, hyperglycemia led to a 5-fold increase in cortical and hippocampal Aβ deposition, strengthening prior evidence that diabetes promotes AD progression derived from AD-prone rodent models.[13] However, this model cannot discriminate between the respective effects of hyperglycemia and insulin deficiency.

Specific T2DM pharmacotherapies may help reduce AD risk. Intranasal insulin has been shown to reduce Aβ accumulation and tau phosphorylation in animal models and appears promising in early clinical studies for enhancing memory and cognitive function in participants with MCI and AD.[12,14] Notably, however, these beneficial effects of intranasal insulin may be attenuated in individuals with an APOE4 allele.[14] Although both E4 carriers and noncarriers with AD exhibit aberrant brain insulin signaling, E4 carrier status appears to modulate the relationship between peripheral and brain insulin metabolism, as well as responses to intranasal insulin.[8] Preclinical and some early clinical evidence supports neuroprotective roles for other T2DM medications, including glucagon-like peptide-1 receptor agonists (GLP1RAs), dipeptidyl peptidate-4 inhibitors, and metformin. For example, GLP1RA treatment and GLP1 overexpression improve cognition, protect neurons from Aβ oligomer-induced toxicity, and reduce brain Aβ deposition in animal models.[12,14]

Some epidemiologic studies have stratified individuals with T2DM by severity of hyperglycemia, often using HbA1c as an index of mean blood glucose, and they suggest that higher HbA1c may predict greater risk of AD.[14] However, this strategy has several key limitations, including the highly variant relationship between HbA1c and mean blood glucose across individuals, inability of HbA1c to capture glycemic variability, and reduced reliability of HbA1c in a broad spectrum of clinical conditions. Notably, longitudinal studies using intensive glucose-lowering or behavioral interventions in individuals with T2DM so far have failed to demonstrate AD risk reduction.[14] These findings raise the question of whether the association between hyperglycemia and AD is not causally direct but rather mediated by a shared, underlying pathophysiology.[4,10] Alternatively, reduction of AD risk may not be evident in the absence of complete normalization of glycemia, which is rarely achieved with current T2DM pharmacotherapy.

Obesity

In epidemiologic studies, the prevalence of obesity in T2DM varies widely, from ~20–90%, with findings that vary based on the clinical definition utilized and nationality of the studied population.[15] Prospective studies have identified midlife but not late life obesity as a risk factor for cognitive decline, all-cause dementia, and AD.[1,16] The adipokines leptin and adiponectin correlate positively and negatively, respectively, with white adipose tissue mass, and share ubiquitous expression of their cognate receptors, including in the brain.[12,14] Leptin is a key neuromodulator that mediates not only food intake and energy expenditure but, further, has been shown in preclinical and in vitro models to exert neuroprotective effects through promotion of axonal growth, synaptogenesis, and neurogenesis, as well as suppression of Aβ formation.[12,14] Clinical studies to date examining associations between peripheral and cerebrospinal fluid concentrations of these adipokines with AD have been limited in part by enrollment of older adults, some with existing MCI or AD.[12] As obesity constitutes a risk factor for AD specifically when present during midlife, the potential pathogenic roles of these adipokines must be examined much earlier, decades prior to the onset of clinical symptoms.

Changes in immune cell phenotype within adipose tissue have been observed with obesity and strongly implicated in the evolution of insulin resistance. The link between obesity and AD has been ascribed in part to an increase in the generation of peripheral cytokines that increase blood-brain barrier permeability, cross the blood-brain barrier, and promote glial cell activation and neuronal insulin resistance.[12,14] Potentially consistent with this model, increased blood-brain barrier permeability and glial cell activation have been observed in patients with AD.[12,14] The growth hormone (GH)/IGF-1 axis is among the key metabolic regulators linking nutrient sensing and immunomodulation. Changes in GH/IGF-1 signaling occur in the setting of obesity, particularly with increased visceral adiposity[17]; thus, altered GH/IGF-1 signaling is evident in both obesity and AD, suggesting another potential mechanistic link among obesity, T2DM, and AD.[5] Indeed, GH/IGF-1-based treatments have been proposed for both obesity and AD, and IGF-1 has been shown to inhibit amyloid precursor protein phosphorylation in vitro and thereby could attenuate Aβ deposition.[5]

Diet and physical activity

Health-related behaviors, including diet and physical activity, have been shown to modify AD risk. Among commonly recommended dietary patterns, the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet have been most extensively studied, and all prescribe a reduction in saturated fat intake.[18] Observational data from both cross-sectional and longitudinal studies support that higher adherence to all three diets associates with reduced risk of cognitive decline and all forms of dementia, including AD.[18] Conversely, high intake of saturated fat and cholesterol can induce insulin resistance and is a risk factor for AD.[18] Free fatty acids readily enter the brain, and saturated fatty acids have been shown to activate astrocytes and promote tau and Aβ polymerization in vitro.[19] Intermittent fasting and ketogenic diets more recently have garnered attention for their potential therapeutic value to both mitigate metabolic dysregulation and reduce AD risk.[3]

Clinical data also support greater physical activity as a protective factor for AD.[16] Remarkably, one meta-analysis of 16 prospective studies found a relative risk for AD of 0.55 (95% confidence interval: 0.36–0.84) for AD among individuals with the highest versus lowest levels of physical activity.[1] Based on these and similar data, sedentariness has been estimated to impart a relative risk of 1.82 for AD.[1] Thus, dietary and exercise habits that predate the diagnosis of T2DM, as well as behavioral changes undertaken as a result of diagnosis, may strongly influence subsequent risk of cognitive decline and AD.

COMORBID CONDITIONS OF T2DM

Depression

Major depression and depressive symptoms are common among individuals with diabetes, with an estimated prevalence of 12% for major depression and 15–35% for milder forms of depression or depressive symptoms.[20] Presence of

diabetes confers a 1.4–3-fold risk of depression, and, notably, depression is also a risk factor for diabetes, underscoring the bidirectional relationship between these conditions.[20] Further, rates of recurrent and treatment refractory depression are exceedingly high among individuals with diabetes.[20]

Depression independently increases the risk of cognitive dysfunction and dementia, conferring a roughly twofold risk of any form of dementia.[1] The links among T2DM, depression, and AD may derive in part from the extensive cross-talk between central serotonin and insulin. These neuromodulators colocalize throughout the brain, and their downstream signaling pathways converge at phosphatidylinositol-3-kinase.[11] Nonetheless, adequate treatment of major depression may not be sufficient to attenuate risk of cognitive decline and AD,[1] just as optimal glycemic control has not been shown to reduce AD risk. These findings again support the intriguing possibility that depression and T2DM may not cause AD, but rather the co-occurrence of these diseases reflects parallel processes in the brain and periphery that differentially manifest as a function of age and individual susceptibility.

Hypertension

The prevalence of hypertension in individuals with T2DM exceeds 50%, and many studies have shown a prevalence greater than 60–75%.[15] The presence of diabetes contributes to arterial blood vessel remodeling and hypertension, and hypertension, in turn, markedly elevates the risk of diabetes-related vascular complications.[15] Relative to individuals with either T2DM or hypertension alone, those with both conditions exhibit increased arterial stiffness, more hypertrophic vessel remodeling, and greater tissue ischemia, in part due to concurrent microvascular disease that reduces maximal tissue perfusion even in the absence of obstructive atherosclerosis.[21] Insulin-mediated effects, including increased sympathetic outflow, greater renal sodium re-absorption, and endothelial dysfunction have been proposed to underlie hypertension specifically in individuals with T2DM.[10]

Hypertension at midlife is a risk factor for both vascular dementia and AD,[1] highlighting the overlap in the etiopathogenesis of these diseases. The neurovascular model of AD indeed postulates that AD is primarily driven by cerebrovascular disease and blood-brain barrier dysfunction.[22] Hypertension contributes to impaired vasodilatation, atherogenesis, and endothelial dysfunction in the cerebrovasculature, all of which contribute to reduced cerebral blood flow, acute and chronic brain ischemia, and blood-brain barrier dysfunction.[22] Reduced cerebral blood flow and blood-brain barrier dysfunction synergistically lead to decreased Aβ clearance and increased Aβ fibrillization, with subsequent amyloid deposition in both brain parenchyma

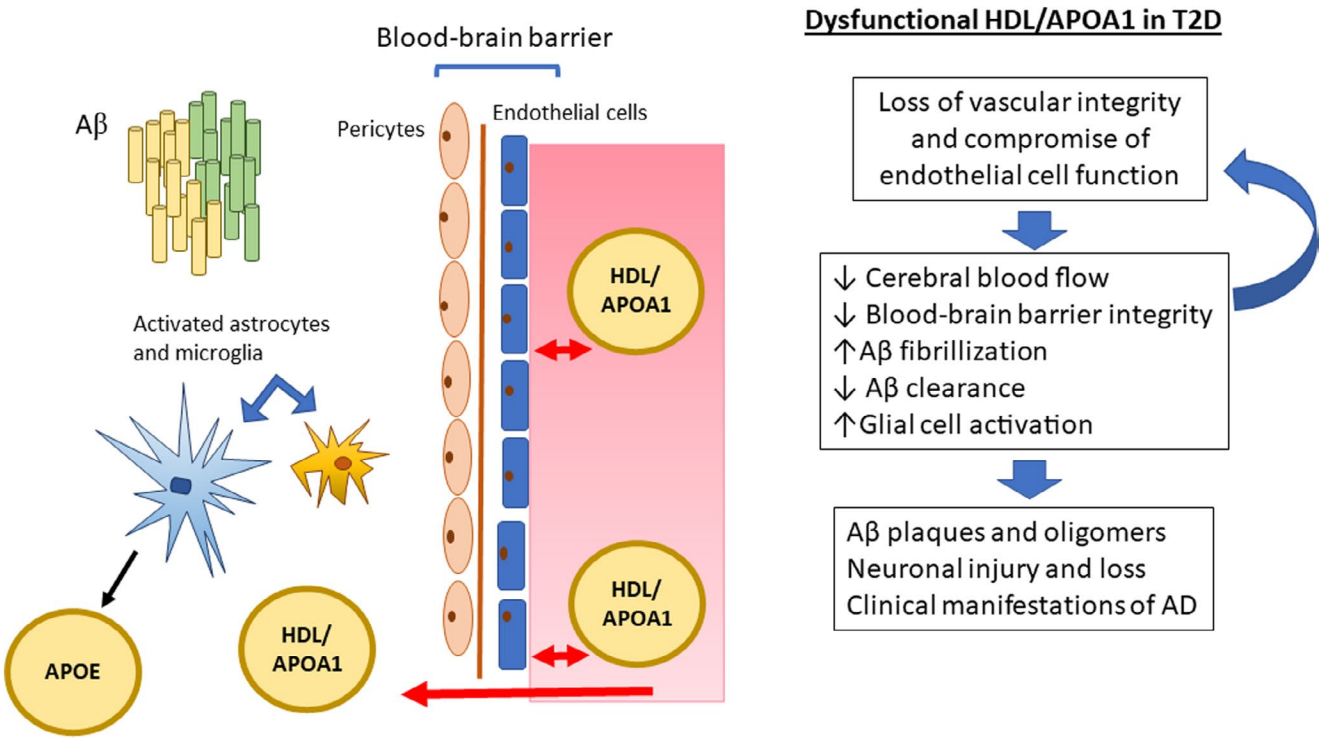

FIGURE 3 APOA1 and APOE play synergistic roles in promoting neurovascular health and inhibiting central amyloid beta (Aβ) deposition. High-density lipoprotein (HDL)/APOA1 dysfunction consequent to type 2 diabetes mellitus (T2DM) could contribute to Alzheimer's disease (AD) pathology through multiple mechanisms, including compromise of blood-brain barrier integrity, loss of APOA1-mediated Aβ clearance and inhibition of Aβ fibrillization, and reduced cerebral blood flow[25]

TABLE 1 Suggested metrics and tools for enhanced phenotyping of individuals with type 2 diabetes

	Relevant clinical and research tools and metrics
Disease pathogenesis	
Insulin resistance	Homeostasis model assessment-insulin resistance (HOMA-IR) index Euglycemic insulin clamp
Insulin deficiency	Need for exogenous insulin C-peptide concentration Hyperglycemic clamp (β-cell function)
Hyperglycemia	Continuous glucose monitoring metrics: • Time above range (>180 mg/dl, >250 mg/dl) • Median glucose
Glycemic variability	1,5-anhydroglucitol Continuous glucose monitoring metrics: • Time in range • Time below range (<70 mg/dl, <55 mg/dl) • %Coefficient of variation
Diet quality	Diet quality surveys Dietary recall assessments
Physical activity	Actigraphy
Obesity	Total and visceral adiposity Leptin and adiponectin concentrations Circulating cytokine and C-reactive protein concentrations Growth hormone/IGF−1 axis dysfunction
Pharmacotherapy	
Insulin	Use of agent Units of insulin/kg body weight Route of administration
Glucagon-like peptide 1 receptor agonists	Use of agent
Dipeptidyl peptidate−4 inhibitors	Use of agent
Metformin	Use of agent
Comorbid conditions	
Depression	History of major depression Depression severity Number of episodes
Cognitive decline	Neuropsychiatric testing Advanced brain imaging
Hypertension	Blood pressure control Number of required medications
Dyslipidemia	Triglyceride concentration HDL-C concentration LDL particle number HDL particle function and non-cholesterol composition

Note: Potential tools and metrics that could be used to clinically and biochemically phenotype individuals with type 2 diabetes in clinical studies. Enhanced phenotyping could better delineate the mechanisms underlying the relationship between type 2 diabetes and Alzheimer's disease and, accordingly, facilitate generation of targeted interventional strategies.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IGF, insulin-like growth factor-1; LDL, low-density lipoprotein cholesterol.

and blood vessels that further exacerbates vascular integrity, neuronal injury, loss of synapses, and glial cell activation.[23] Thus, the highly prevalent co-occurrence of T2DM and hypertension does not merely reflect the presence of two distinct risk factors for AD but rather a distinct context of accelerated vascular disease that can directly promote the evolution of AD. Promisingly, intensive blood pressure control in older adults reduced the rate of incident MCI and nonsignificantly reduced the primary outcome of dementia.[24]

Dyslipidemia

The prevalence of dyslipidemia in individuals with T2DM varies between 30% and 90% depending on the study population, with a characteristic pattern of elevated plasma triglyceride concentration, low high-density lipoprotein cholesterol (HDL-C) concentration, and small, dense low-density lipoprotein particles.[19] To date, epidemiologic studies linking diabetes-related dyslipidemia and AD risk have yielded inconsistent findings.[6]

One potential reason for these inconsistent findings is the predominant focus on HDL-C content, as plasma HDL-C concentration fails to capture many of the vasoprotective functions of HDL particles and their primary protein constituent apolipoprotein A-I (APOA1). Metrics of HDL/APOA1 function as opposed to HDL-C content may better predict vascular risk. APOA1 crosses the blood-brain barrier and exerts neuroprotective effects (Figure 3).[25] Therefore, T2DM-related dyslipidemia could entail functional changes in HDL/APOA1 that directly contribute to AD pathology.

CONCLUSION

T2DM and AD are highly complex disorders that rather may constitute clinical syndromes with variable underlying diseases. Recognition of this physiologic and phenotypic complexity is essential for elucidating the relationships between T2DM and AD. Future work also

is needed to better characterize potential interactions between discrete facets of T2DM and age, female sex, and presence of APOE4, the strongest risk factors for late-onset AD. Clinical studies, both interventional and observational, would benefit from expanded use of metrics that increase the homogeneity of study cohorts and therefore better test both the association of discrete facets of T2DM with AD risk and the therapeutic effects of targeted interventions within clearly defined patient populations. This work will be facilitated by the increasingly widespread use of continuous glucose monitoring in the management of T2DM, which provides more comprehensive insight into glycemia than HbA1c alone (Table 1). Careful clinical history, laboratory assessments, and glucose clamp techniques also provide critical clinical and biochemical context for interrogating the relationships between specific facets of T2DM pathogenesis and treatment and AD risk. Finally, use of neuroimaging and more sensitive measures of cognitive decline may be necessary to discern effect sizes given the long latency between exposure and development of frank dementia for many of these risk factors. Comprehensive clinical phenotyping promises greater mechanistic understanding of the metabolic and vascular pathways that link T2DM and AD. This understanding is critical for identifying individuals at greatest risk for AD and developing targeted treatment strategies to mitigate this risk.

CONFLICTS OF INTEREST

The authors declare no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.J.H. and K.B.R. wrote the manuscript.

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