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REVIEW

Sweet Solutions: Unlocking the Diabetes-Dementia Connection for Better Outcomes

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Type 2 diabetes and Alzheimer's dementia represent important health challenges in our society today. Understanding the relationship between these conditions is crucial. This article explores the research on whether they share common risk factors or if they may influence each other's development, which could lead to more effective prevention and treatment strategies.

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Type 2 diabetes (T2D) and Alzheimer's dementia (AD) are the most pressing epidemics of our time. Whether these two conditions are coincidental and parallel phenomena arising from similar overlapping risk factors or if synergistic diseases somehow link the two is being debated.[1]

Diabetes mellitus is one of the leading causes of death in the United States[2,3] (Figure 1) and the future projection of the diabetes epidemic in our aging, growing, and increasingly overweight population is even more alarming.[4] While the mortality of T2D has been slowly improving in high-income countries,[5] the disease remains associated with significant morbidity and increased mortality.[6] Advances in diabetes have reduced adverse outcomes from some vascular (traditional) complications (ie, CAD, stroke, etc), but evidence shows an increased burden of a different set of lesser-known, "non-traditional" complications[7] (ie, cancer, infections, liver disease, heart failure, functional disability, affective disorders, or cognitive decline and dementia).

This article focuses on cognitive decline, as dementia is becoming the most significant epidemic of our time alongside T2D. The article investigates the potential links between AD and T2D and explores the possible insurance implications of recent advancements in AD.

THE SURGE IN DEMENTIA

Mirroring the diabetes trend, dementia rates have also been rising. With our aging and growing population, dementia cases worldwide are anticipated to surge dramatically. Currently, Alzheimer's dementia (AD) is the sixth leading cause of death in the United States (Figure 1).[2,3] Around 6.7 million Americans aged 65 or older have AD, projected to nearly double in the coming decades.[8] Globally, the affected population is expected to reach

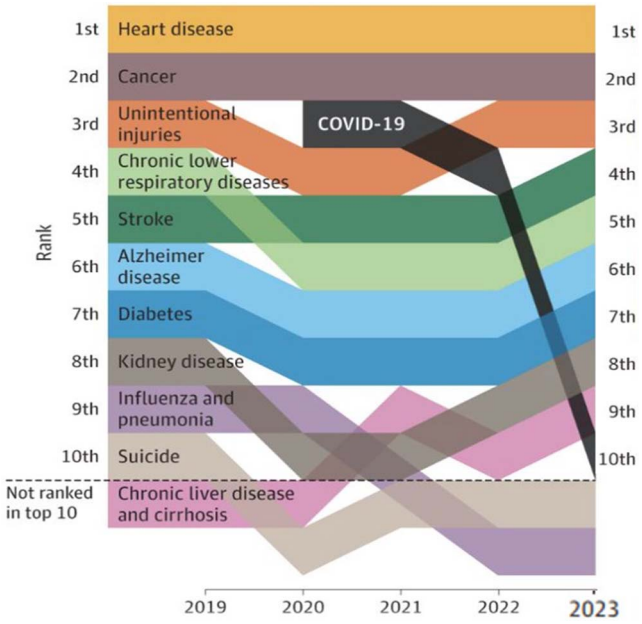

Figure 1. *Leading causes of death and shifting trends -US, 2019-2023.*[2]

100-150 million. The impact on quality of life and life expectancy is profound.

Dementia is characterized by irreversible cognitive decline. AD is the most common type of dementia - accounting for about 60%-80% of all cases. It can often coexist with other types of dementia, particularly vascular dementia.

AD has numerous risk factors,[8] and T2D substantially increasing the risk of not only cerebrovascular disease and stroke but also late-onset AD. *New evidence suggests that midlife, but not late-life, diabetes onset increases the risk of dementia.*[9]

On the other hand, a significant portion of people with dementia also have diabetes, suggesting overlapping risk factors with T2D. The escalating dementia trend underscores the urgent need for increased awareness, research for timely recognition, effective treatment, and sufficient resources to combat this debilitating condition.

ALZHEIMER'S DISEASE & THE GENETIC CONNECTION

AD is a progressive neurodegenerative disorder that ultimately destroys various cognitive functions and abilities secondary to brain cell loss. The first neurons damaged are those in parts of the brain responsible for memory, language, and thinking (judgments and insight), with changes in behavior and physical deterioration occurring in later stages.[8] Despite being discovered over a century ago, the root cause remains elusive. The disease is marked by toxic protein deposits, (extracellular beta-amyloid plaques and intracellular protein tau neurofibrillary tangles), leading to cell damage, cell death, and brain atrophy. These core pathological hallmarks are now believed to drive and signal the disease but likely do not directly cause it. Recent research reveals contributing roles of genetics and inflammation in AD development,[1,8] both of which are discussed below.

Familial Alzheimer's dementia with early onset (<1% of AD cases) follows an autosomal dominant pattern, while late-onset AD (age >65 years) has a polygenic background. Recent research (on several genes) has identified a strong genetic risk factor and a novel link between the late-onset AD and the APOE ε4 isoform.[8]

About 55% of Alzheimer's patients carry at least one copy of this apolipoprotein E (APOE) gene variant. Having one or two copies of the gene multiplies the likelihood and risk of development of AD. However, carrying the APOE ε4 isoform does not mean that an individual will inevitably develop dementia, indicating the importance of gene-environment interactions. Modifying risk factors could prevent or delay nearly half of dementia cases,[9] even in individuals with higher genetic risk.

EARLY DETECTION – OPPORTUNITIES AND CHALLENGES

Alzheimer dementia typically progresses through stages over several years before noticeable symptoms develop (Figure 2).[8] Currently, overt symptoms prompt the investigations which lead to the medical diagnosis. There is no cure for the disease; only disease-modifying therapies are available.

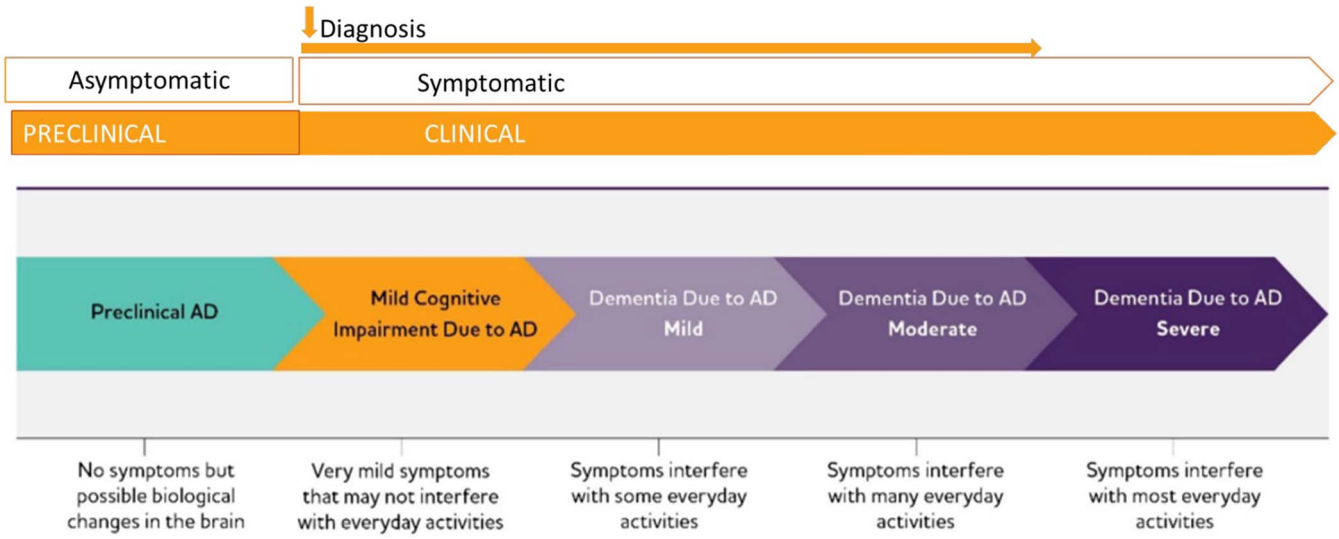

Figure 2. *Stages of Alzheimer's disease. Continuum shows components are not representative of duration, Ref. 8 (Modified picture).*

In preclinical Alzheimer's disease, individuals may have measurable brain changes that indicate the earliest signs of AD, but they have not yet developed symptoms. The long latent phase of 15-20 years (silent stage) could offer a window for timely intervention, not only with potential future medications but with preventive and proactive lifestyle changes – following the mantra of "eat well, move more, stress less, and love more and, specifically, by limiting risk factors and implementing intensified lifestyle changes that can potentially prevent or alter the course of the disease. Examples include regular moderate exercise, meditation, and yoga-based or other stress management, whole foods and a plant-based diet low in fat and sugar, taking certain daily supplements,[10] learning "new" skills, and engaging in activities with friends and families.

As a result of breakthrough research, it is hoped that preclinical AD can be detected from a single drop of blood using biomarkers *before* its debilitating effects take hold.[11-13] Digital biomarkers (mobile or wearable technology) or artificial intelligence (ie, brain-imaging, voice recognition, etc) may also play a role in early detection or *prediction* of cognitive decline.[14,15] The recent success of anti-amyloid immunotherapy trials in symptomatic AD has increased the enthusiasm for testing this strategy.

While timely detection of AD offers significant benefits, it raises important and relevant concerns, including ethical, psychological, and discriminatory worries.

ALZHEIMER DISEASE – TYPE 3 DIABETES?

AD and T2D share several pathophysiological features (Figure 3), most notably insulin resistance (IR).[1,16,17] Peripheral IR is well

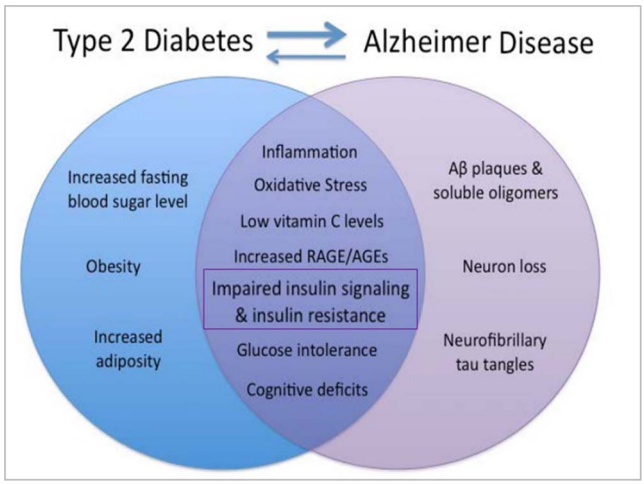

Figure 3. *Shared features of Type 2 Diabetes and Alzheimer's disease (Ref. 16).*

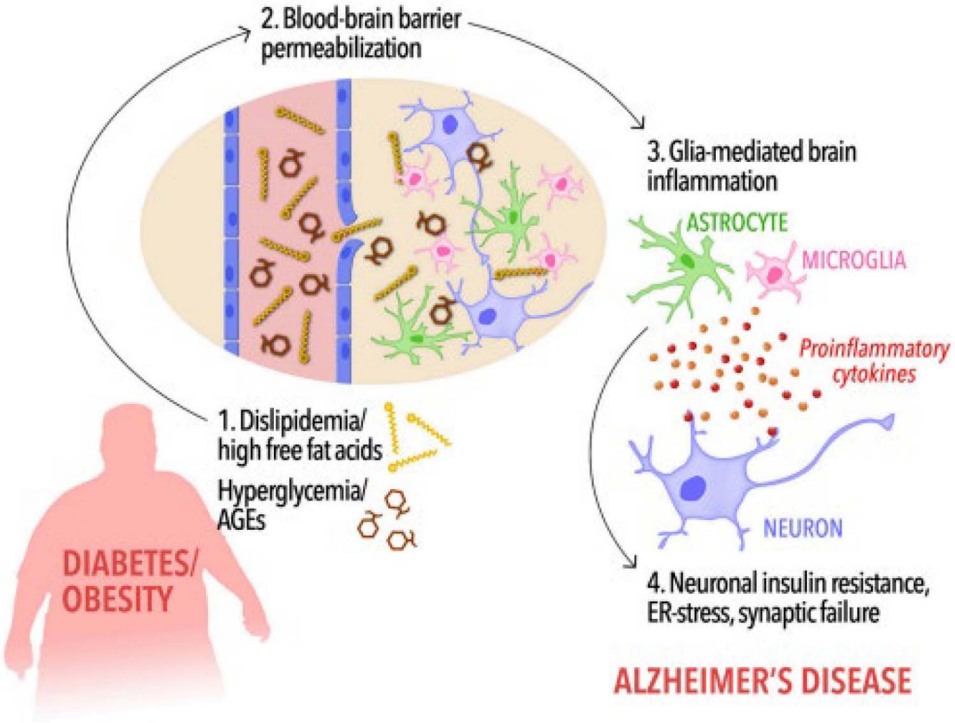

Figure 4. *In diabetic and obese individuals, dyslipidemia, elevated free fatty acids (FFAs), hyperglycemia, and increased advanced glycation end-products (AGEs) can: 1) increase blood-brain barrier (BBB) permeability, 2) allow FFAs to enter the brain. This disrupted BBB, combined with high brain FFAs and AGEs, triggers microglia and astrocyte activation, 3) leading to the release of proinflammatory cytokines. Chronic low-grade brain inflammation subsequently causes insulin resistance in neurons, 4) contributing to cognitive impairment and Alzheimer's disease (Ref. 22).*

known in T2D. Brain IR is age-related, but diabetes, especially with longer duration and with suboptimal control, fuels the development of brain IR. IR can be defined as the failure of cells to respond to insulin, resulting in impairments in various important functions. Brain cells are highly dependent on insulin and glucose. Insulin, intact insulin signaling, and glucose are vital for neuron's survival, synapse formation, memory, and other cognitive and emotional functions. Centers of memory and learning are particularly affected as they are highly dependent on insulin and glucose. The toxic protein clumps, characteristics of AD, enhance the brain insulin resistance. This effect is further intensified in the presence of APOE ε4 (by interfering with the brain insulin receptors and its machinery).[17,18]

The close association and connection between these two conditions (T2D and AD) have led to Alzheimer's disease being referred to as "Type 3" diabetes.[17,19,20] The term, however, is *not* a medical diagnosis, it is rather a research expression, highlighting the relationship between metabolic dysfunction and brain health.[1]

NEUROINFLAMMATION

The role of inflammation in AD pathogenesis and the role of blood brain barrier (BBB)[21] in inflammation has been recently recognized. In T2D, high blood sugar and associated blood products can damage the blood-brain-barrier (BBB), which normally protects the brain from harmful substances (Figure 4).[22] When the BBB is disrupted, toxic blood products can enter the brain triggering immune responses and activating the brain's immune cells (microglia).[22] Normally, microglia maintain brain health by removing waste and toxins, particularly during sleep. However,

for example, in this context, they promote chronic neuroinflammation,[21] which escalates brain insulin resistance and neurodegeneration. Chronic neuroinflammation boosts the development of brain insulin resistance (IR), neurodegeneration, and the progression of Alzheimer's disease. The presence of the APOE ε4 genotype escalates the inflammatory process and the disease's pathology.

A KEY QUESTION

The connection between T2D and AD raises the question: Can anti-diabetic medications help combat AD? New research aims to repurpose or reposition certain diabetes medications, particularly GLP1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i).

Initial research with 2 to 3 years follow-up has shown encouraging results.[9,23-26] Clinical trails show that these medications may protect the brain, improve cognitive function, and reduce dementia incidence (compared with placebo) to a degree that exceeds expectations from glucose control and weight loss alone, with cognitive benefits emerging even before significant weight loss occurs. While most clinical trials are still relatively small, larger trials are now underway[27] to advance Alzheimer's research.

Another superpower of these diabetes and obesity drugs is their ability to suppress inflammation.[28] The promise of GLP1RA and SGLT2i therapies extends well beyond diabetes and weight loss. These medications have independently been approved for various conditions, including heart failure and CKD. Cognitive decline is a new area of research. One of the most important unifying roots in benefits in these conditions is "taming inflammation." Their benefits in dementia also include gains from vascular protection, reduced oxidative stress, improved insulin signaling, and the overall cardiovascular improvement also contributes to positive outcomes in dementia.

SUMMARY - CURRENT REALITIES VS NEW HOPES

Type 2 Diabetes and Alzheimer's disease are leading epidemics of our time with overlapping risk factors and mechanisms. The root cause of Alzheimer's cases is still mostly unknown, and recent discoveries about the connection between APOE ε4 gene and neuroinflammation offer new insights. Because timely identification of Alzheimer's disease is paramount for effective management and prevention, detecting AD in its preclinical (silent) stage is a promising screening opportunity, but it also brings controversies. The strong link between T2D and AD serves as a basis to investigate whether newer diabetic treatments can slow dementia progression. In this exciting new area of research with substantiated early hopes, there is still a ways to go and further studies are necessary to confirm their full potential.

IMPLICATIONS FOR LIFE AND DISABILITY INSURANCE UNDERWRITING

A significant portion of life and disability insurance applicants suffer from diabetes, and this number is rising. Underwriting diabetes using current underwriting manuals might seem simple, but this perception arises from our traditional approach. However, Diabetes is a complex disease with a shifting landscape of complications.

The combination of decreasing mortality and increasing prevalence has increased the overall mean years lived with diabetes. New factors are influencing diabetes outcomes, including the underrecognized impact of AD on morbidity and mortality. Upcoming novel treatments (disease-modifying strategies like GLP1RA and SGLT2i therapy) may mitigate some concerns. However, their therapeutic potential has yet to be confirmed.

These impacts may be anticipated across various business domains, such as underwriting, pricing, product development, claims,

and underwriting manuals. Awareness of the changing landscape of diabetes complications can assist in refined pricing prediction and risk assessment. It can facilitate in depicting early signs or signals and identify individuals who are at an increased risk for cognitive decline – clients older than 65 with a long history and sub-optimally controlled diabetes and/or with multiple ill-managed cardiovascular risk factors, and/or carrying the APOE ε4 gene, even without presenting concerning symptoms.

Carriers could leverage the benefits of the predictive power of various biomarker testing, and the utilization of artificial intelligence, allowing opportunities for specific new insurance products. However, in addition to the benefits of the early detection of Alzheimer's dementia in the asymptomatic stage, this could potentially bring controversy to the table with ethical, psychological, and discriminatory concerns.

Overall, breakthroughs in research promise a brighter future for dementia care, highlighting the need for insurers to stay informed about these developments and to prepare for the various changes they may bring.

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