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Acceleration Of Brain Aging And Cognitive Decline Due To Type 2 Diabetes Mellitus

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Abstract

Introduction: This review delves into the impact of Type 2 Diabetes Mellitus (T2DM) on cognitive decline and accelerated brain aging, addressing the critical need for understanding the complex interplay between diabetes and neurological outcomes.

Methods: A systematic search of electronic databases (PubMed, MEDLINE, Google Scholar) was conducted using predefined keywords, including "Type 2 Diabetes Mellitus," "cognition," and "brain aging." Inclusion criteria encompassed peer-reviewed research articles, clinical studies, and reviews in English, with manual reference list checks performed to include relevant studies. Data extraction involved systematic retrieval of key study elements from selected articles.

Results: T2DM, characterized by a diverse array of symptoms, exhibits a particularly alarming manifestation in the form of accelerated brain aging, leading to cognitive decline. Notably, T2DM is associated with a 50% increased risk of dementia. Comprehensive evaluations, including studies analyzing the UK biobank dataset, reveal a 26% faster gray matter atrophy in T2DM patients compared to normal aging. This atrophy is most pronounced in the ventral striatum and is notably associated with executive function decline.

Conclusion: In conclusion, T2DM emerges as a substantial contributor to accelerated brain aging and cognitive decline, with implications for both males and females. The severity of neurological decline is influenced by factors such as disease duration, glycemic control, and age. Despite advancements, the exact pathophysiology linking T2DM to brain atrophy and cognitive decline remains elusive, underscoring the need for further research. Additionally, the absence of specific biomarkers emphasizes the importance of regular neurological screenings for early detection and intervention.

INTRODUCTION

Diabetes mellitus (DM) is defined as a metabolic disorder that for which hyperglycemia is a characteristic presentation.[1]

Brain aging is a process that starts early in life and advances with growing age. On the pathophysiological level, it's characterized by the shrinking of neuron cells, their degeneration, and demyelination along with small vessel diseases. Further, it's associated with activation of microglia, slow metabolism, and formation of white matter lesions. Morphologically, brain aging leads to cerebral atrophy, cortical thinning, ventricular enlargement, loss of gyrification, and degradation of white matter.([2] , [3]) Cognitive function is a vast term that refers to mental processes involving memory, learning, perception, attention, making decisions, and language skills.[4] It has been noted that type 2 diabetes mellitus is linked to a decline in cognitive function compared to those without diabetes.([5] , [6]) Cognitive decline and brain aging in those with T2DM are associated with increased duration of diabetes and poor glycaemic control. Patients with T2DM have increased brain aging, i.e., cerebral atrophy, and loss of grey and white matter. These structural changes are said to be caused by diabetes-related risk factors like hypertension, glycaemic control, duration of diabetes, and retinopathy.[6] Overall, reports show that T2DM accelerates cognitive decline that is typically associated with the brain's normal aging process.[7] In our study, our objective is to analyze the effect of diabetes on brain aging and cognitive decline. We aim to find the correlation and exact mechanisms behind T2DM and the decline in cognition.

Type 2 DM represents close to 90% of diabetes cases. In this condition, there is a reduced response to insulin, termed insulin resistance. Initially, the body compensates for this resistance by increasing insulin production to regulate glucose levels. However, over time, insulin production declines, leading to the development of Type 2 diabetes mellitus (T2DM) ([8], [9]).

The following factors contribute to the development of T2DM, Insulin resistance when muscle, fat, and liver cells don't use insulin well, which leads to insulin resistance. As a result, the pancreas makes more insulin to support glucose entering cells. Over time, the pancreas cannot make enough insulin, and blood glucose levels rise. In pancreatic dysfunction, the pancreas cannot make enough insulin to keep blood sugar situations within a healthy range. Exactly why this happens isn't known. Genetics Having a close relative with T2DM, like as a parent, or family, increases the threat of developing the condition. Weight, being overweight or obese is a main threat factor for developing T2DM. The fat distribution also plays a part. Physical inactivity Lack of physical exertion is another important risk factor for developing T2DM.([8] , [9])

DM type 2 mostly develops in people over age 45, but nowadays children, teens, and young adults are also developing it especially if they have some of the risk factors such as being obese, smoking, and genes.([10] , [11])

The prevalence of type 2 DM is rising in both sexes; however, men are more commonly diagnosed at an earlier time period in their life and have comparatively lower body fat mass than women. Slightly more men than women have diabetes mellitus.[12]

Cognition refers to the processes involved in acquiring knowledge and comprehension through thought, experience, and sensory input mentally. It encompasses a wide array of advanced intellectual functions and processes, including but not limited to knowledge acquisition, attention, planning, decision-making, memory retention, reasoning, judgment formation, perception, appreciation, language comprehension, and visuospatial abilities, among others ([13]).

Numerous different cognitive tests check for cognitive impairment. They generally involve answering questions and doing simple tasks, similar to repeating lists of words or spelling words backward. The most generally used tests generally take 15 minutes or less. Cognitive impairment is more common among aged people, but it's not a normal part of aging. It can be caused by multiple medical and mental health conditions.([14] , [15])

Various cognitive assessments are employed to detect cognitive impairment, typically comprising tasks such as answering questions and performing simple exercises, like reciting word lists or spelling words in reverse. These tests, commonly administered within 15 minutes or less, are widely utilized. While cognitive impairment is more prevalent among older individuals, it is crucial to recognize that it is not an inherent aspect of aging. Rather, it can arise from diverse medical and mental health conditions ([14], [15]).

Some diseases and conditions can cause a decrease in cognition, such as Alzheimer's disease because it affects memory, thinking, and behavior, also Parkinson's disease can cause a decrease in cognition because it causes memory loss and difficulty with executive function, traumatic brain injury, stroke, depression cause memory loss, difficulty with attention and concentration, and problems with executive function.([13] , [15] , [16])

Type 1 diabetes (T1DM) manifests as an autoimmune disorder characterized by the immune system's assault on the pancreatic beta cells responsible for insulin production ([36], [39]).

Consequently, there is an insufficient supply of insulin, a pivotal hormone for blood sugar regulation ([36]). This condition is identified as a T cell-mediated autoimmune ailment ([35]). While genetic susceptibility notably influences its onset, environmental factors, including viral infections, are also implicated in its etiology ([36], [37]).

On the other hand, Type 2 diabetes primarily arises from insulin resistance.[38] The body's cells become less responsive to the effects of insulin, which means that even though the pancreas produces insulin, it's not as effective in allowing glucose to enter the cells.[38] Over time, the pancreas may struggle to produce enough insulin to meet the body's needs.[38] Genetic factors, along with lifestyle elements like poor diet, lack of exercise, and obesity, are key contributors to the development of Type 2 diabetes.([36] , [38])

Autoimmune diseases are conditions in which your immune system mistakenly damages healthy cells in your body.[37] Type 1 diabetes is one of the most common autoimmune diseases, where the immune system destroys insulin-producing cells in your pancreas.([37] , [39])

Common Symptoms for Both Types:

Polyuria: Excess glucose in the blood leads to increased urination as the kidneys work to filter and remove it. ([40] , [42] , [44] , [45])

Polydipsia (Excessive Thirst): Frequent urination results in dehydration, triggering a sense of excessive thirst.([40] , [42] , [44] , [45])

Polyphagia: Cells, deprived of glucose, signal a need for more food156.

Type 1 Specific Symptoms:

Rapid Onset: Type 1 diabetes often manifests rapidly, with severe symptoms appearing over a short period.([40] , [41] , [42] , [44])

Type 2 Specific Symptoms:

Gradual Onset: Type 2 diabetes symptoms may develop gradually and go unnoticed for a long time, which can delay diagnosis.([40] , [42] , [43] , [44])

Treatment Approaches:

Type 1 Diabetes:

Insulin Therapy: Individuals with Type 1 DM need exogenous insulin to replace the hormone their body can't produce. Multiple daily injections or insulin pumps are common methods.([30–34], [45])

Type 2 Diabetes:

Lifestyle Modifications: This includes adopting a balanced diet, regular exercise, and maintaining a healthy weight. These changes can improve insulin sensitivity and glucose control.([31], [32], [45])

Oral Medications and Insulin:

Depending on the severity of T2DM, medications that enhance insulin sensitivity or stimulate insulin production may be prescribed. In some cases, insulin therapy might be necessary.([32], [34], [45])

Prognosis and management

Type 1 DM is a chronic condition that requires lifelong management with insulin therapy, blood sugar monitoring, and lifestyle modifications.([37], [38]) Technological advancements in insulin pumps and continuous glucose monitors have significantly improved the quality of life for individuals T1DM is often accompanied by numerous complications, encompassing cardiovascular disease, renal issues, neuropathy, and vision impairments ([35], [36]). Shockingly, nearly half of individuals with T1DM will encounter a significant complication during their lifetime ([37]). However, for those who manage to navigate the initial 20 years post-diagnosis without complications, the prognosis remains promising ([37]). To mitigate the risk of complications, it is imperative to remain well-informed about T1DM and seek out supportive communities ([37]).

Type 2 DM, on the other hand, is the most common form of diabetes and often requires substantial lifestyle changes for effective management.[40] With diligent self-care and medical supervision, individuals can achieve and maintain good blood sugar control.[40] Long-term complications like cardiovascular disease, kidney problems, neuropathy, and vision issues can be mitigated or delayed with consistent management.[40] However, untreated chronic high blood sugar can cause severe complications that are usually irreversible and can shorten lifespan.[40] The prognosis for diabetes varies greatly depending on several factors, including age, genetics, and race.[40]

Overall, both Type 1 and Type 2 DM require consistent management and lifestyle modifications to prevent complications and maintain good health. However, with proper care, individuals with diabetes can lead healthy, fulfilling lives.

Cognition represents the intricate mental journey of acquiring knowledge and insight through contemplation, experience, and sensory input. This encompassing process encompasses a spectrum of sophisticated intellectual activities and functions, including attention, memory, decision-making, reasoning, perception, language, and visuospatial abilities, among others ([41], [45]).

The term 'cognitive deficits' serves as a broad descriptor, encapsulating the impairment across various cognitive domains. It's essential to note that cognitive deficits aren't confined to specific diseases or conditions; rather, they may manifest as a component of an individual's underlying health state. 'Cognitive deficit' is often used interchangeably with 'cognitive impairment,' and it can manifest as either a transient state or a progressive, enduring condition ([42])."

Several factors can affect cognition, including age, medications, depression, thyroid disorders, and substance abuse. These factors have the potential to influence cognition by disrupting typical brain structure and function, resulting in cognitive changes that encourage ongoing drug use through maladaptive learning and other mechanisms.([41] , [42])

Conditions and diseases that can affect cognition include mild cognitive impairment (MCI) and dementia. Drugs that can affect cognition include medications and substance abuse. The mechanism by which these conditions, diseases, and drugs affect cognition is by disturbing the usual brain structure and function, these factors induce cognitive changes that foster persistent drug use via maladaptive learning and various other mechanisms.([41] , [42])

The main sign of mild cognitive impairment is a slight decline in mental abilities. Examples include forgetfulness, difficulty with language, trouble with spatial relationships, and poor judgment. Patients who are usually affected by cognitive decline are those who are aging, have thyroid disorders, or depression, or are taking medications that can cause cognitive impairment. ([41] , [44])

The prognosis associated with cognitive deficits varies depending on the underlying causative factors. These factors can range from medication usage to conditions like depression or thyroid disorders ([41]). Notably, in some cases, individuals with mild cognitive impairment (MCI) may experience a reversal to normal cognitive functioning or maintain stability. Conversely, instances exist where cognitive impairment attributed to medications may result in a misdiagnosis of MCI ([44]). Therefore, it's imperative for individuals undergoing cognitive changes to promptly seek professional evaluation for accurate diagnosis and potential intervention.

Currently, the U.S. Food and Drug Administration (FDA) has not sanctioned any medications specifically designed to address mild cognitive impairment. Nevertheless, treatment plans encompassing non-pharmacological interventions are available to enhance cognitive function ([44]).

In summary, cognition represents a multifaceted mental process encompassing diverse aspects of high-level intellectual functions and processes. Numerous factors, such as age, medications, depression, thyroid disorders, and substance abuse, can influence cognition. Conditions and diseases such as mild cognitive impairment (MCI) and dementia can also impact cognitive function. The prognosis of cognitive deficits hinges on the underlying cause, emphasizing the importance of timely intervention for diagnosis and potential treatment.

METHODOLOGY

Study Design:

This review article aims to analyze the effect of Type 2 Diabetes Mellitus (T2DM) on cognitive decline and accelerated brain aging.

Data Sources and Search Strategy:

We conducted a systematic search of electronic databases (PubMed, MEDLINE, Google Scholar) using keywords such as "Type 2 Diabetes Mellitus," "cognition," and "brain aging." Manual reference list

checks were performed to include relevant studies.

Inclusion and Exclusion Criteria:

We included peer-reviewed research articles, clinical studies, and reviews in English that investigated the relationship between T2DM and cognitive decline or reported on brain aging in T2DM. Duplicate or irrelevant studies were excluded.

Data Extraction:

We systematically extracted data from selected studies, including study objectives, participant characteristics, design, key findings, and statistical analyses.

Data Synthesis:

A qualitative analysis of selected studies' findings was performed to identify themes related to T2DM's impact on cognition and brain aging.

Ethical Considerations:

No ethical considerations were applied as this review analyzed existing literature without human participants or original data collection.

RESULTS

Although diabetes mellitus has a wide array of symptoms, the most alarming one has been the acceleration of brain aging which leads to cognitive decline. T2DM has also been associated with a 50% increased risk of dementia. There have been several studies that have evaluated the impact of T2DM on cognitive function.[6] Brain aging is characterized by cell, tissue, and organ level damage and deterioration processes that lead to morphological brain shape changes.[3]

In this paper, we aim to find out the different mechanisms in diabetes that lead to cognitive decline. Some such mechanisms are due to hyperglycemia which leads to inflammation and oxidative stress which damages the blood vessels in the brain causing neuronal dysfunction. Insulin is important for brain function and its dysfunction can impair cognitive processes. Diabetes can also cause blood vessel damage which increases the risk of strokes and inflammation. Frequent episodes of hypoglycemia can also harm the brain and impair cognitive function.

A study conducted utilizing the UK Biobank dataset revealed that individuals with Type 2 Diabetes Mellitus (T2DM) experience gray matter atrophy at a rate 26% faster than that observed in normal aging. The research also involved the extraction of cognition data encompassing five cognitive domains: abstract reasoning, executive function, processing speed, reaction time, and numeric memory ([7]). Particularly noteworthy were the pronounced effects observed in executive function, with a 1.9% decline in performance noted per year. Additionally, severe atrophy of the ventral striatum was observed. These findings strongly corroborate the presence of neurocognitive impairments in T2DM patients, primarily characterized by structural atrophy. Notably, the study highlighted that the severity of neurocognitive effects is exacerbated with prolonged disease duration, with consistent observations across genders. The comparison across sample sizes was facilitated through the use of structural MRI, functional MRI, and cognitive testing methodologies.

This article is founded upon an extensive review of existing literature. Notably, the studies referenced in this article exhibit diverse inclusion criteria and limitations, contributing to potential variability in findings. For instance, in the investigation utilizing the UK Biobank, female subjects who were non-menopausal and undergoing hormone therapy were excluded. Additionally, individuals with diabetes who self-reported an age of onset exceeding 40 years were included in the study ([7]). One notable challenge encountered during the research process was the absence of HbA1c measures, which would have offered a direct assessment of disease severity. This limitation underscores the importance of considering the constraints inherent in the available data when interpreting the study's outcomes.

DISCUSSION

This review sheds light on the intricate relationship between Type 2 Diabetes Mellitus (T2DM) and cognitive decline, emphasizing the accelerated brain aging observed in affected individuals. The comprehensive analysis draws from a systematic search of electronic databases and inclusion criteria encompassing peer-reviewed articles and clinical studies in English. The discussion synthesizes key findings from diverse studies, offering valuable insights into the mechanisms underlying T2DM-related cognitive impairment.

The findings presented in this article underscore the concerning link between T2DM and an elevated risk of cognitive decline, with a notable 50% increase in the risk of dementia among affected individuals. It is crucial to recognize that brain aging involves complex processes spanning cellular, tissue, and organ levels, resulting in structural alterations in the brain. This study aimed to elucidate the diverse pathways through which T2DM contributes to cognitive impairment, including inflammation and oxidative stress induced by hyperglycemia, vascular damage, insulin dysfunction, and the potential repercussions of recurrent hypoglycemic episodes.

A significant aspect of this review involves the analysis of data from the UK Biobank, which revealed a striking 26% acceleration in gray matter atrophy among T2DM patients compared to the natural aging process. The study assessed various cognitive domains, such as abstract reasoning, executive function, processing speed, reaction time, and numeric memory, highlighting a noteworthy 1.9% annual decline in executive function. Structural atrophy, particularly in the ventral striatum, was strongly linked to T2DM, with more pronounced effects observed in individuals with longer disease durations.

Nevertheless, it is essential to acknowledge the limitations inherent in the studies cited, including variations in inclusion criteria and the absence of direct measures of disease severity, such as HbA1c levels in certain instances. The exclusion of specific demographic groups and inconsistencies in measurement methodologies across studies may affect the generalizability of the findings.

CONCLUSION

In conclusion, T2DM leads to an increased rate of brain aging and cognitive decline compared to the normal population. Grey matter atrophy in such patients was 26% more rapid than seen with normal aging. Moreover, greater duration of disease, poor glycemic control, and older age were associated with more severe neurological decline. These effects were similar in both males and females.([6] , [7]) T2DM has also been linked with a 50 – 100% increased risk of dementia in elderly patients. Chronic hyperglycemia and microvascular complications like diabetes retinopathy also hasten brain aging.[6] With regards to cognitive function, the commonly affected domains are those of information processing speed, concentration, attention, working memory, and executive functioning. Additionally, diabetes possesses a 1.25-1.9 higher risk for cognitive decline. Several mechanisms explaining the interconnection between T2DM and its neurological effect have been proposed. However, no definite pathophysiology has been established. One such mechanism is chronic hyperglycemia-mediated neuronal damage that is caused by the production of AGEs (Advanced Glycation End Product) leading to the release of pro-inflammatory cytokines and ultimately causing inflammation.[6] Another factor is that increased insulin resistance affects cerebrovascular mechanisms for cognitive impairments in diabetes.([6] , [17]) It is hence, essential to elucidate the exact pathogenesis behind T2DM-associated brain atrophy and cognitive decline.

Currently, there are no specific biomarkers for diabetes-induced cognitive decline. Therefore, awareness regarding the risks of cognitive decrement must be spread and regular neurological screening should be supported. More studies with long-term follow-up with neurological imaging and assessments are required to effectively early diagnose, treat, and prevent T2DM-induced brain damage.

DECLARATION

Ethical Statement

The research conducted in this study has received approval from the Institutional Review Board/Ethics Committee at Ivane Javakhishvili Tbilisi State University. All procedures performed in this study involving human participants were in accordance with the ethical standards of Ivane Javakhishvili Tbilisi State University and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

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Conflicts of Interest

The authors maintain that there are no conflicts of interest related to this research. Neither financial nor non-financial competing interests are present.

Data Availability

The data supporting the findings of this study are comprehensively presented within the article and its supplementary materials. For any additional data, interested parties may request access, and such requests will be considered.

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