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ASSOCIATION BETWEEN OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN PATIENTS WITH ALZHEIMER'S DISEASE AND TYPE II DIABETES

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ABSTRACT

The Type 2 Diabetes Mellitus (T2DM) and Alzheimer disease (AD) are two of the most common chronic diseases among aging populations in the majority of developed countries globally and are beginning to be considered biologically related disorders. Epidemiological data prove that patients with T2DM are at a very high risk of getting AD, which results in the newly emerged notion of Alzheimer's disease as Type 3 Diabetes, which is a cerebral insulin resistance and brain glucose metabolism disruption. This review examines the common molecular pathways in which AD and T2DM comorbidity interact, focusing especially on oxidative stress and mitochondrial impairment as key actors of neurodegeneration. Overwhelming reactive oxygen species (ROS) production, mitochondrial bioenergetic dysfunction, calcium imbalances and insulin signal dysfunction have a vicious cycle that causes neuronal injury, amyloid-beta deposition and tau hyperphosphorylation to escalate. Also, oxidative stress, neuroinflammation, and impaired mitochondria are further amplified by advanced glycation end products (AGEs) and activation of the AGERAGE signaling axis. The review also discusses the role of disturbed mitochondrial dynamics, impaired mitophagy and neuroinflammatory reactions of microglia and astrocytes in progressive cognitive decline. New therapeutic approaches that address mitochondrial activity, oxidative stress, insulin resistance and metabolic homeostasis such as mitochondrial-targeted antioxidants, antidiabetic drugs, natural polyphenols and multi-target combination therapies are mentioned as potential remedies to disease pathology. Knowledge of the metabolicneurodegenerative interface of AD and T2DM is a crucial way to comprehend the pathogenesis of the disease, as well as to find new opportunities in early prevention, individual approach to treatment, and enhanced cognitive activity.

Keywords: *Alzheimer's disease; Type 2 Diabetes Mellitus; Oxidative stress; Mitochondrial dysfunction; Insulin resistance; Neuroinflammation; Advanced glycation end products (AGEs)*

INTRODUCTION

The most common neurodegenerative disorder, and a major worldwide wide-spreading phenomena, is the issue of Alzheimer disease (AD), as it is responsible in majorities of the cases of dementia in populations of the elderly. It is a

progressive neurological disorder that is typified by a unique clinical syndrome, which is progressive cognitive impairment, memory loss, behavior, and eventually loss of functional autonomy. It does not only have an individual patient impact but also on the families and healthcare systems of those patients causing significant socioeconomic burdens on a global scale.[1] Neuropathological characteristics of the Alzheimer disease are well known, they include formation of extra-cellular deposition of amyloid-2 (plaques) as well as intracellular deposits (neurofibrillary tangles) of hyperphosphorylated tau protein, severe loss of synapses and neurons especially in the parts of the brain that are important in learning and memory such as the cerebral cortex and the hippocampus . Although the pathophysiology of the Alzheimer disease has been extensively investigated over the decades, the etiology of the disease is yet to be fully comprehended and the existing therapeutic interventions are rather symptomatic and lead to only slight improvements in cognition without stopping the progression of the disease. The lack in this knowledge highlights the urgent importance of further research on the underlying molecular and biochemical pathways behind the process of neurodegeneration in AD.[2]

Type II diabetes mellitus (T2DM) is a long-term metabolic condition that is associated with the insulin resistance, impaired insulin secretion, and chronic hyperglycemia. It has become one of the most widespread non-communicable diseases in the world, with the number of its victims reaching hundreds of millions of people and subjecting the health and financial systems of health care around the world to enormous costs. Type II diabetes has long-term effects that are far-reaching and are associated with a vascular, renal, ophthalmologic and neurological variety of effects. Notably, an accumulating epidemiological and clinical data has shown that there is a major relationship between T2DM and cognitive impairment and people with Type II diabetes exhibit a greater occurrence of dementia, earlier cognitive decline, and faster rates of Alzheimer pathology progression. This increased awareness of the diabetes-neurodegeneration nexus has led scientists to inquire into the general pathogenic mechanisms underlying these two seemingly distinct disease entities. The hypothesis that metabolic dysfunction can play a significant role in neurodegenerative mechanisms has had a paradigm shift in our thinking about both disorders and has created a new avenue of research.[3]

The close and reciprocal interrelationship between oxidative stress and mitochondrial dysfunction represents perhaps the most critical mechanistic link between Alzheimer's disease and Type II diabetes mellitus. Excessive ROS production can directly damage mitochondrial membranes, critical enzymes of the electron transport chain, and mitochondrial DNA, leading to progressive impairment of respiratory chain function and energy production. Conversely, dysfunctional mitochondria generate increased levels of ROS during their failed attempts at energy production, amplifying oxidative stress throughout the cell. This reciprocal interaction creates a self-perpetuating and pathologically amplifying cycle that progressively accelerates cellular injury and disease advancement.[4]

In Alzheimer's disease, this cycle may specifically enhance amyloid-β aggregation, tau hyperphosphorylation, and synaptic loss, while in T2DM it may worsen insulin resistance and metabolic dysregulation. Emerging research has additionally highlighted the role of impaired insulin signaling in the brain as a shared pathological feature of AD and T2DM. Insulin is essential for multiple critical neuronal functions including neuronal survival, synaptic plasticity, neurotransmitter synthesis, and cognitive function. In Alzheimer's disease, reduced insulin sensitivity and altered insulin receptor signaling have been consistently observed, leading to the increasingly accepted concept of Alzheimer's disease as "Type III diabetes" . Insulin resistance in the brain is closely mechanistically linked to mitochondrial dysfunction and oxidative stress, further supporting the compelling evidence for mechanistic overlap between these two disorders.

LITERATURE REVIEW

Smith et al. (2020) carried out pioneer research on the Alzheimer disease that formed the basic knowledge about this neurodegenerative disorder as the principal cause of dementia in the whole

world. Their efforts revealed that Alzheimer disease is described as a progressive decline in cognitive abilities, memory, behavioral imbalances, and ultimate loss of functional independence in sufferers. The authors determined and reported the neuropathological markers of the disease, such as extracellular accumulation of amyloid- 2 plaques and intracellular neurofibrillary tangles which are made up of hyperphosphorylated tau protein as well as marked loss of synapses and cell death especially in the hippocampus and the cerebral cortex. In spite of all the research that was carried out, their work also demonstrated that the etiology of the Alzheimer disease is still not fully understood, and further research into the molecular mechanisms of the disease underpinning it is still needed.[5]

Abu Khadra et al. (2019) in their study, in Jordan, investigated the oxidative stress markers in Type II diabetes mellitus patients in a cross-sectional study. They also found high malondialdehyde (MDA), one of the main lipid peroxidation products, and a significant reduction in antioxidant enzyme activity, especially catalase, in diabetic subjects compared with healthy ones. These results indicated that there exists a strong oxidative imbalance typical of the diabetic condition, which shows strong evidence that oxidative stress is a central pathogenic mechanism in T2DM and not only an epiphenomenon of hyperglycemia. The researchers underlined that oxidative stress is a pathogenic factor of cell damage in diabetes, and mitochondria have become the primary endogenous source of ROS.[6]

Rovira-Llopis et al. (2015) performed significant studies outlining the quality control errors in the mitochondrion during diabetes-associated neurodegenerative disease. They used comparative observational study to show that disturbed mitochondrial structure and dynamics are significant factors leading to oxidative stress and dysfunction in the cells, especially in the insulin-resistant brain. The study found that there were drastic changes in the mitochondrial enzymes involved in the normal functioning of the mitochondria and, more importantly, correlated these pathological changes with insulin resistance markers. Their reports were a powerful indicator of the importance of mitochondrial impairment in the pathology of T2DM as well as a possible process that links diabetes to neurodegeneration.[7]

Maragkou et al. (2025) carried out a systematic review regarding the oxidative stress and mitochondrial dysfunction in Alzheimer disease. Their overall analysis revealed that the level of reactive oxygen species and reactive nitrogen species in affected brain is highly increased leading to extensive oxidative stress to the vital cellular macromolecules such as lipids, proteins, and nucleic acids. Notably, this work did determine that these oxidative modifications do not only precede the classical neuropathological appearances of AD but they also dynamically interact with amyloid and tau pathogenesis, which may worsen the disease progression. Their study enhanced the idea that oxidative stress is an early and eminent phenomenon in the development of AD.

Another study by Veselov et al. (2023) has expanded the scope of the research and highlighted cross-relationships between metabolic disorders and Alzheimer disease. Their efforts highlighted the similarity of the two diseases in that they also share pathophysiological mechanisms such as insulin resistance, excessive oxidative stress, and mitochondrial dysfunction as being equally relevant to the processes of the two diseases. Their examination offered valuable insight into the conceptual framework associating these ostensibly separate disorders via shared molecular pathways, and the hypothesis that metabolic dysfunction can facilitate neurodegeneration.[8]

As Azhar et al. (2017) emphasized, mitochondrial impairment and oxidative stress are common pathophysiological mechanisms that may explain the mechanistic relationship between mitochondrial impairment and Type II diabetes mellitus comprehensively. Their study put forward the fact that these were not just coincidental associations but an underlying biological overlap in the pathogenesis of diseases. The researchers presented evidence that a better understanding of these common mechanisms could result in better diagnostic and therapeutic approaches that could be applied to both conditions, especially in patients who have both diseases.[10]

MATERIAL AND METHODS

This descriptive review study evaluated the association between oxidative stress and mitochondrial dysfunction in Alzheimer's disease and Type II diabetes mellitus over four months. Peer-reviewed articles were sourced from PubMed, Google Scholar, ScienceDirect, and SpringerLink. Included studies involved participants aged ≥50 years, focused on the relevant conditions or biomarkers, and reported measurable biochemical outcomes. Excluded were non-full-text articles, case reports, editorials, conference abstracts, unrelated disorders, duplicates, and studies lacking methodological detail or relevant outcomes. No sample size was required for this review.

MAIN BODY

1. INTRODUCTION AND EPIDEMIOLOGICAL OVERVIEW

Type 2 Diabetes Mellitus (T2DM) and Alzheimer disease (AD) are the two prevalent chronic conditions in aging populations in the world and the socioeconomic and community health implications of these diseases are colossal. Growing epidemiological and mechanistic data suggests that these diseases are intensely biologically related at the utmost even though they are believed to be different entities in the past. T2DM patients are much more prone to cognitive decline and dementia and epidemiological research confirms that people with T2DM are nearly twice as likely to have AD. This fascinating association has driven researchers to postulate AD as Type 3 Diabetes and emphasize the significance of insulin resistance and metabolic dysfunction of the brain in the event of neurodegradation.[11]

Table 1. Epidemiological and Pathophysiological Links Between Alzheimer's Disease (AD) and Type 2 Diabetes Mellitus (T2DM)

Aspect	Alzheimer's Disease (AD)	Type 2 Diabetes Mellitus (T2DM)	Shared Features / Connection
Disease Nature	Neurodegenerative disorder	Metabolic disorder	Increasingly interconnected diseases
Global Impact	Leading cause of dementia	Major metabolic epidemic	High socioeconomic burden
Risk Relationship	Cognitive decline and neurodegeneration	Nearly doubles AD risk	AD conceptualized as "Type 3 Diabetes"
Key Metabolic Issue	Cerebral insulin resistance	Peripheral insulin resistance	Impaired glucose metabolism
Protein Pathology	Amyloid-β plaques and tau tangles	Metabolic protein modification	Misfolded protein accumulation
Energy Metabolism	Reduced brain glucose utilization	Chronic hyperglycemia	Energy homeostasis disruption
Oxidative Stress	Elevated ROS in neurons	ROS generated by hyperglycemia	Central pathogenic driver
Mitochondrial Function	Impaired ATP production	Defective mitochondrial metabolism	Shared mitochondrial dysfunction
Vulnerable Populations	Aging populations	Metabolically at-risk groups	Genetic and environmental influences
Disease Outcome	Synaptic loss and cognitive decline	Systemic metabolic damage	Accelerated neurodegeneration

2. MOLECULAR MECHANISMS LINKING OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN AD AND T2DM

Reactive oxygen species is an important crossroad between metabolic impairment and neurodegeneration in AD and DM. The main producers of endogenous ROS, mitochondria, are ironically the major producers of cellular energy via oxidative phosphorylation. In the course of normal aerobic respiration, the oxidation of electrons in the electron transport chain, especially at complexes I and III, is intercepted by oxygen molecules, forming superoxide anions, and, consequently, other ROS such as hydrogen peroxide and hydroxyl radicals. Although physiological production of ROS plays a role in critical cell communication and redox homeostasis, an overproduction of ROS, known as oxidative stress, leads to catastrophic destruction of cellular macromolecules such as proteins, lipids, and nucleic acids.[12]

Table 2. Molecular Mechanisms Linking Oxidative Stress and Mitochondrial Dysfunction in AD–T2DM

Mechanism	Molecular Events	Effects on Mitochondria	Pathological Outcome
ROS Overproduction	Electron leakage from ETC (Complex I & III)	Oxidative damage to proteins, lipids, DNA	Cellular dysfunction
Hyperglycemia-Induced ROS	Excess glucose metabolism & NADPH oxidase activation	Increased mitochondrial stress	Chronic oxidative environment
Amyloid-β Toxicity	Direct mitochondrial membrane interaction	Loss of membrane potential	Impaired respiration
Tau Hyperphosphorylation	Disrupted mitochondrial trafficking	Reduced mitochondrial dynamics	Synaptic dysfunction
Calcium Dysregulation	ROS alters calcium channels	Calcium overload in mitochondria	mPTP opening
mPTP Activation	Cytochrome c release	Mitochondrial depolarization	Apoptosis initiation
Synaptic Mitochondrial Damage	Increased oxidative sensitivity	Reduced neurotransmitter release	Cognitive decline
ATP Production Failure	Impaired oxidative phosphorylation	Energy depletion	Neuronal degeneration
Feedback Loop	ROS ↔ Calcium amplification	Progressive dysfunction	Accelerated neurodegeneration

3. INSULIN RESISTANCE AS A CENTRAL HUB: FROM TYPE 2 TO TYPE 3 DIABETES

The idea of Type 3 Diabetes is based on the understanding that AD is typified by massive insulin resistance in the brain, which closely resembles, but is not identical to peripheral insulin resistance in T2DM. Besides its established metabolic actions, insulin also has important neuromodulatory activities in the brain, such as the modulation of synaptic plasticity, memory consolidation, and neuronal survival. The evidence of functional impairment in brain insulin and insulin-like growth factor (IGF) signalling pathways are known mediators of dysregulated energy metabolism, and the drivers of the AD neurodegeneration cascade.[13]

Chronic hyperglycemia and peripheral hyperinsulinemia in T2DM disrupt cerebral glucose metabolism in a variety of ways. High peripheral glucose levels substitute that of glucose

across the blood-brain barrier, decreasing the brain glucose supply. Further, the presence of a high concentration of circulating insulin competes with amyloid-beta (Abb) with insulin-degrading enzyme (IDE) to favor pathological Abrs deposition in AD brains. Neuroimaging experiments indicate that cerebral glucose metabolic rate decreases decades prior to the development of clinical symptoms of AD, and as such, metabolic dysfunction is an early pathological process.[14]

Figure 2: Insulin resistance impairs neuronal function

6. THERAPEUTIC STRATEGIES TARGETING OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

A number of traditional systemic antioxidants have failed to pass the pathetic clinic trails in AD largely due to bad experimental penetration through blood brain barrier, low bioavailability and distribution characteristics. New therapy methods use mitochondrial-conjugated antioxidants that are conjugated to lipophilic triphenylphosphonium cations and provide specific protection to the centres of mitochondrial ROS production. These agents are superior in preclinical AD and T2DM models and they safeguard Complex I activity, preserve mitochondrial membrane potential and mitigate cognitive decline.[15]

Besides mitochondrial bioenergetics-supportive strategies, there can be mitochondrial bioenergetics-protective strategies. Ketones bodies that are assisted by ketogenic diets enter the blood-brain barrier and provide complementary energy to facilitate mitochondrial ATP production and reduce the development of ROS, which can address the flaws of glucose metabolism in the AD brains. It has been demonstrated that nicotinamide adenine dinucleotide (NAD+) supplementation enhances ATP generation in the mitochondrion and activates sirtuin-mediated mechanisms of stress resistance, which is cognitive beneficial in preclinical AD models.[16]

Table 3. Therapeutic Strategies Targeting Oxidative Stress and Mitochondrial Dysfunction in AD–T2DM

Therapeutic Strategy	Target Mechanism	Mode of Action	Expected Benefit
Mitochondrial-Targeted Antioxidants	Excess ROS	Accumulate within mitochondria to neutralize ROS	Protect mitochondrial integrity
Ketogenic Metabolic Support	Glucose metabolism deficit	Provide ketone bodies as alternative fuel	Improved ATP production
NAD^+ Supplementation	Bioenergetic decline	Activates stress-resistance pathways	Enhanced mitochondrial function
Metformin (AMPK activation)	Insulin resistance	Promotes mitochondrial biogenesis	Reduced Aβ and tau pathology
GLP-1 Receptor Agonists	Impaired insulin signaling	Improve neuronal insulin sensitivity	Reduced neuroinflammation
DPP-4 Inhibitors	GLP-1 degradation	Enhance endogenous incretin signaling	Neuroprotection in AD-T2DM
Natural Polyphenols	AGE formation & ROS	Antioxidant and anti-inflammatory actions	Improved mitochondrial health
AGE-RAGE Inhibitors	AGE signaling axis	Block inflammatory pathways	Reduced oxidative stress
Mitophagy Enhancement	Damaged mitochondria accumulation	Activate PINK1-Parkin pathway	Cellular quality control
Combination Therapies	Multi-pathway pathology	Target metabolic + mitochondrial defects	Improved cognitive preservation

The multiplicity of AD-T2DM pathophysiology is further raising concerns that unifocal interventions could become ineffective to achieve significant clinical value. Multi-target therapies that concurrently target several pathological pathways, such as oxidative stress, mitochondrial dysfunction, AGE-RAGE signaling, and neuroinflammation, are more effective in preclinical models. Integrating antidiabetic drugs with mitochondrial-targeted antioxidants, natural compounds, lifestyle interventions, and cognitive training have demonstrated superior therapeutic efficacy in preclinical and early clinical trials.

The new paradigm focuses on the use of tailored medicine, classifying patients according to genetic considerations, biomarkers of oxidative stress and mitochondrial dysfunction, and metabolism to optimally select therapy and dose them to maximize cognitive retention.[17]

7.1: CONCLUSION(S)

Mitochondrial dysfunction and oxidative stress form a critical pathophysiological link between Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). In AD, oxidative stress impairs mitochondria, leading to neuronal loss, synaptic damage, and cognitive decline through ROS-mediated damage, calcium dysregulation, bioenergetic failure, and AGE-RAGE-driven neuroinflammation. Recognizing AD as a metabolic disorder (type 3 diabetes) with brain insulin resistance and mitochondrial failure opens new therapeutic avenues. Emerging evidence suggests that mitochondrial-targeted agents and antidiabetic drugs, which reduce oxidative stress, AGE accumulation, and metabolic dysfunction, are less toxic and may slow AD progression, especially in T2DM patients. Translating these mechanistic insights into clinical practice requires well-designed, long-term trials to assess cognitive preservation in at-risk populations. Understanding these molecular pathways further

clarifies disease mechanisms in AD-T2DM comorbidity.

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