

Review Article

Metabolism: A Novel Shared Link between Diabetes Mellitus and Alzheimer's Disease

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As a chronic metabolic disease, diabetes mellitus (DM) is broadly characterized by elevated levels of blood glucose. Novel epidemiological studies demonstrate that some diabetic patients have an increased risk of developing dementia compared with healthy individuals. Alzheimer's disease (AD) is the most frequent cause of dementia and leads to major progressive deficits in memory and cognitive function. Multiple studies have identified an increased risk for AD in some diabetic populations, but it is still unclear which diabetic patients will develop dementia and which biological characteristics can predict cognitive decline. Although few mechanistic metabolic studies have shown clear pathophysiological links between DM and AD, there are several plausible ways this may occur. Since AD has many characteristics in common with impaired insulin signaling pathways, AD can be regarded as a metabolic disease. We conclude from the published literature that the body's diabetic status under certain circumstances such as metabolic abnormalities can increase the incidence of AD by affecting glucose transport to the brain and reducing glucose metabolism. Furthermore, due to its plentiful lipid content and high energy requirement, the brain's metabolism places great demands on mitochondria. Thus, the brain may be more susceptible to oxidative damage than the rest of the body. Emerging evidence suggests that both oxidative stress and mitochondrial dysfunction are related to amyloid- β ($A\beta$) pathology. Protein changes in the unfolded protein response or endoplasmic reticulum stress can regulate $A\beta$ production and are closely associated with tau protein pathology. Altogether, metabolic disorders including glucose/lipid metabolism, oxidative stress, mitochondrial dysfunction, and protein changes caused by DM are associated with an impaired insulin signal pathway. These metabolic factors could increase the prevalence of AD in diabetic patients via the promotion of $A\beta$ pathology.

1. Introduction

As a chronic metabolic disease, diabetes mellitus (DM) is one of the most important public health challenges in the 21st century. DM is broadly characterized by elevated levels of blood glucose, mainly caused by insufficient insulin production or unresponsiveness of the body to insulin. According to the latest data from the International Diabetes Federation (IDF, <https://www.diabetesatlas.org/>), there are 425 million people with diabetes in the world, and one in 11 adults worldwide is diagnosed as having DM. By 2045,

the number of people with DM is expected to increase to 629 million. Recent epidemiological studies have shown that some diabetic patients are more susceptible to dementia than healthy individuals [1–4]. In addition, mounting statistical and biological data support a correlation between DM and dementia [5–9], which may share common cellular and molecular mechanisms.

Based on a recent report from the World Health Organization (WHO), approximately 50 million people worldwide have dementia. Although there are over 100 types of dementia, the most well-known form is Alzheimer's disease (AD),

which accounts for 50%-75% of all cases. AD can damage cells and nerves interrupting the transmitters that convey information in the brain, particularly those responsible for memory storage. Generally, gradual memory loss is the first symptom of AD, but other signs include difficulty in finding the right word, correctly identifying other people, and solving problems [10–12]. In addition, the majority of AD cases frequently suffer from multiple complications (e.g., DM, other neurodegenerative disorders, cardiovascular diseases, and renal diseases). These comorbidities can enhance the complexity that underlies AD pathogenesis [13–15].

Until recently, studies have suggested that these complications may be associated with AD pathogenesis and memory loss [16–18]. Among the various complications, DM has been shown to be the most influential in the development of AD [13, 14]. Epidemiological studies of AD in diabetic patients from the past decade are shown in Table 1. From these data, we conclude that high AD prevalence in some diabetic populations may be related to insulin resistance and metabolic abnormalities. However, not all individuals with DM develop dementia, and not all dementia cases have DM. DM and AD are two independent metabolic diseases, and both of them are associated with disturbed energy metabolism in the body. Therefore, we speculate that the increased risk of AD in diabetic patients may be partially attributed to metabolic abnormalities. As one of the most basic features of an organism, energy metabolism is a reactive steady-state system that satisfies the energy demands of tissues and organs [19]. Improved understanding of the metabolic associations between DM and AD might provide novel insight into the onset and relationship between both diseases and may at least partly explain the causality.

2. Impaired Insulin Signaling Pathway: The Pathogenesis of AD

Insulin, a peptide hormone produced by the beta cells of the pancreatic islets, is the main anabolic hormone of the body and can regulate the metabolism of carbohydrates, lipids, and proteins. The first step in triggering the insulin signaling pathway is insulin recognizing and binding to a transmembrane tyrosine kinase receptor. This receptor (insulin receptor (IR)) results in the tyrosine phosphorylation of insulin receptor substrates (IRS) by the insulin receptor tyrosine kinase (INSR), thereby blocking downstream signaling pathways such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway. The PI3K/AKT pathway further regulates a number of downstream signaling pathways important for protein synthesis and amyloid- β ($A\beta$) clearance (i.e., through mammalian target of rapamycin (mTOR) signaling) [20]. This pathway also affects the activity of glycogen synthase kinase-3 (GSK-3 β), a major tau phosphorylating kinase and crucial glycogen synthase, which can modulate tau expression [21–23]. In addition, an impaired insulin signaling pathway, $A\beta$ deposition, and mitochondrial dysfunction can interact reciprocally to form a vicious circle. This may explain why diabetic patients are susceptible to AD (Figure 1).

Similar to most organs in the body, the brain is an insulin-sensitive organ, where insulin signaling regulates energy metabolism, cell survival, and cellular homeostasis. Due to its neuroprotective function [24, 25], insulin is beneficial for neuronal growth and survival [26–28]. Over the past few years, accumulating data indicate that insulin regulates the concentration of several neurotransmitters that have essential roles in memory formation, such as acetylcholine, norepinephrine, and epinephrine [29]. Insulin also supports neuronal plasticity and cholinergic functions, which are required for learning, memory, and myelin maintenance. Moreover, damaged insulin signaling in the brain can greatly affect cognitive impairment and neurodegeneration, particularly mild cognitive impairment and AD [30]. Collectively, these observations suggest that insulin is a protective factor for brain function, and insulin signaling is an important pathway in the prevention of cognitive decline.

$A\beta$ is the main component of senile plaques (SPs), which are one of the histopathological markers of AD, and has a vital influence on the progression of neurodegenerative diseases [31]. A previous work has found that pre-proinsulin mRNAs and insulin protein levels are significantly decreased by $A\beta$ -stimulation in astrocytes [32]. Recent postmortem analyses also support the idea that insulin signaling is impaired in AD brains [33, 34]. Furthermore, deficient insulin signals have been observed in mammalian models of AD, in which $A\beta$ is overexpressed or induced by an intracerebral injection [33, 35]. $A\beta$ can also competitively inhibit insulin binding to the IR, which results in the loss of membrane insulin receptors. This is an important contributor to synaptic and dendritic spine damage [36], although there are other factors that contribute to synaptic dysfunction in AD such as oxidative stress, tau phosphorylation, and lipid peroxidation [37–39]. Taken together, these data suggest that $A\beta$ pathology could contribute to insulin signaling destruction and that insulin signaling may be a potential target for the prevention and treatment of AD.

3. Glucose Metabolism Disorder Is a Potential Factor for AD in Diabetic Patients

Compared with energy demand, brain energy storage is limited, and reduced oxygen or glucose availability diminishes brain function. In addition to stored energy, the brain is highly dependent on the glucose supply from the blood, but glucose metabolism in AD is dramatically decreased. This is likely due in part to enzymes involved in glycolysis, the tricarboxylic acid cycle, and ATP biosynthesis [40]. Thus, glucose content may be a reflection of neuronal function, and the ratio of glucose utilization can be used to observe changes of brain activity in various neurodegenerative diseases.

As an important participant in brain compensation for excessive glucose utilization, brain glycogen metabolism functions to guarantee brain energy and neurotransmitter metabolism. In human and rodent studies, DM affected glycogen content in various brain regions [41]. Compared with that of healthy people, the glycogen content in the occipital lobe of patients with type I DM (T1D) is significantly reduced [42], as is GSK-3 β , which is a crucial enzyme in glycogen

TABLE 1: Summary of epidemiological research on DM and AD in recent ten years.

Year	Country	Effective sample size	Case definition		Underlying mechanisms	Reference
			DM	AD/dementia		
2009	Sweden	1248	Being recorded in the inpatient register system, or use of hypoglycemic drugs, or a random blood glucose level ≥ 11.0 mmol/l at baseline (or HbA1c level $\geq 6.4\%$ at second and third follow-up examinations)	Diagnostic and Statistical Manual of Mental Disorders, revised third edition criteria	Glucose dysregulation	[140]
2010	Japan	135	Glucose tolerance test and diabetes-related factors	The Consortium to Establish a Registry for Alzheimer's Disease guidelines and the Braak stage	Insulin resistance	[141]
2011	America	29	American Diabetes Association glycemic criteria for pre-diabetes	Petersen criteria for mild cognitive impairment	Insulin resistance	[142]
2011	China	25393	At least 2 records of DM within one year during 2000–2007 or who had used either sulfonylureas or metformin as oral antidiabetic medication for more than three months	At least 2 records of a diagnosis of dementia within any 1 year during 2000–2007	Oral antidiabetic drugs could decrease the incidence of dementia in T2DM patients	[143]
2013	Japan	175	The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus	The Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition	DM-related metabolic abnormalities	[4]
2017	Israel	363	The American Diabetes Association classification	The Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria	Insulin resistance	[144]
2019	Mexican American	69	Self-reported, HbA1c $> 6\%$	Neuropsychological tests	Cell-free mitochondrial DNA	[145]

synthesis [23]. Moreover, DM can promote glucose transportation by increasing the permeability of the blood-brain barrier (BBB). In some brain regions, insulin is sensitive to glucose transport proteins (GLUT), such as GLUT4 and GLUT8 [43, 44], and phosphorylation events initiated by insulin signaling are able to regulate GLUT4 transporters [45]. In diabetic animal models, glycolytic ability and acetyl-CoA activity were reduced [41, 46], which contributed to mitochondrial dysfunction by decreasing ATP production and promoting reactive oxygen species (ROS)/reactive nitrogen species (RNS) formation (Figure 1). Apolipoprotein E (APOE) is a multifunctional protein with central roles in lipid metabolism, neurobiology, and neurodegenerative diseases. Neuropathological data and clinical trials [47] have shown that the correlation between DM and AD is particularly strong in individuals carrying the APOE4 allele. Individuals with the APOE4 allele also have lower glucose metabolism in the posterior cingulate, precuneus, and/or lateral parietal regions [48]. Accordingly, diabetic patients with anomalous glucose content and metabolic pathways in the brain have an increased risk of AD.

A variety of preclinical models have shown that energy metabolism is closely related to the pathological development of AD. DM can cause glucose transport disorders and metabolic abnormalities in the body, which can in turn lead to cognitive dysfunction. Therefore, therapeutic strategies to

reduce the incidence of AD in diabetic patients should focus on controlling glycemic levels or restoring glucose metabolism. This may also be beneficial in preventive measures designed to delay and slow AD onset and progression.

4. Mitochondrial Dysfunction and Oxidative Stress Are Relevant to the Occurrence and Development of AD in Diabetic Patients

Mitochondria have important physiological functions in the body, including oxidative respiration, energy metabolism, free radical production, and apoptosis [49, 50]. Many studies have shown that mitochondria play an essential role in delaying aging and preventing neurodegenerative diseases [51]. However, due to the abundant energy demand of the brain, it is much more vulnerable to mitochondrial dysfunction [52]. Many studies have further shown that mitochondrial dysfunction is indispensable in the pathogenesis of various diseases such as DM and neurodegenerative disorders [51, 53]. Moreover, oxidative phosphorylation creates ROS as a by-product, which may damage different types of molecules and further increase oxidative stress. Oxidative stress is closely associated with age-related diseases [52], and therefore, mitochondria can be both dangerous and beneficial.

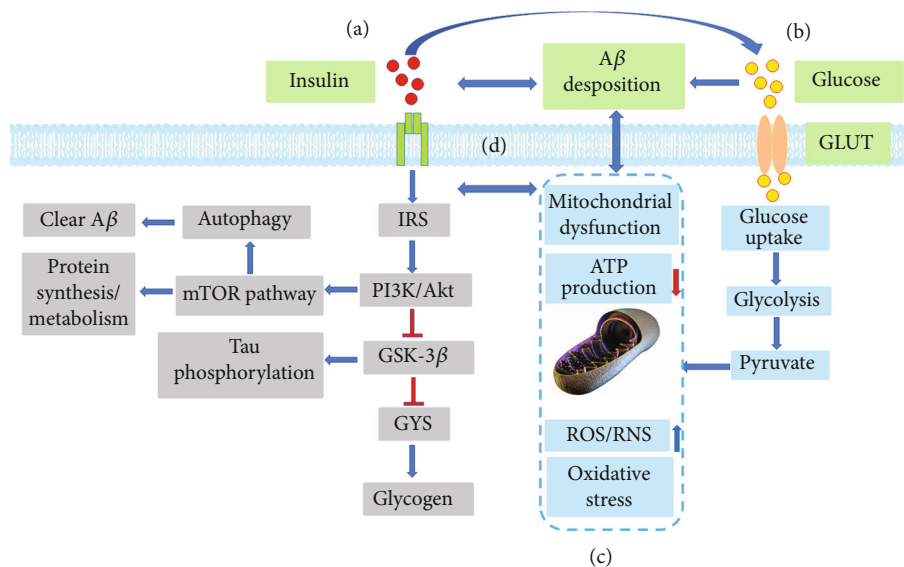


FIGURE 1: Overview of the insulin signaling pathway and relevant mechanisms implicated in AD. (a) Tyrosine phosphorylation of insulin receptor substrates (IRS) allows the association of IRSs with the regulatory subunit of phosphoinositide 3-kinase (PI3K). The PI3K/AKT signaling pathway deactivates glycogen synthase kinase 3 (GSK-3), leading to the activation of glycogen synthase (GYS) and thus glycogen synthesis. In addition, the PI3K/AKT signaling pathway can affect protein synthesis/metabolism and clearance of A β by activating the mTOR pathway. (b) The insulin/insulin signaling pathway can promote glucose transportation by regulating GLUT, and high levels of glucose can lead to A β deposition. (c) Disordered glucose metabolism leads to ROS/RNS formation and decreased ATP production, which is the main manifestation of oxidative stress. Mitochondrial dysfunction can lead to impaired cellular energy production and reduction in insulin secretion and sensitivity. (d) Impaired insulin signaling pathway, A β deposition, and mitochondrial dysfunction promote each other to form a vicious circle.

Dysfunctional mitochondria are less efficient in producing ATP, but more efficient in generating ROS, which could represent a primary cause of the oxidative imbalance observed in AD [54, 55]. It has been demonstrated that the imbalance of mitochondrial division and fusion may give rise to excessive ROS production, dissipation of membrane potential, deficiency in cellular respiratory function, and decreased ATP production [56]. A large amount of ROS will result in a series of common AD pathological alterations, such as oxidative damage of proteins, carbohydrates, and lipids. Nishikawa et al. have shown that increased mitochondrial oxidative stress and ROS production can occur under hyperglycemic conditions [57]. Dysregulated mitochondria can contribute to calcium dyshomeostasis and cause apoptosis and memory impairment [56, 58, 59]. In addition, the accumulation of mtDNA mutations is one reason for electron transport chain abnormalities, which may affect ATP production, destroy brain function, and facilitate the AD occurrence [56, 58, 59]. These mtDNA mutations have been detected in type II diabetes (T2D) patients, while mitochondrial genes are often missing in pancreatic β cells in T2D animal models [60]. Proteins such as peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α), nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 (NRF2), and mitochondrial transcription factor A (TFAM) are involved in mitochondrial biosynthesis and are also strongly related to neurodegenerative disorders [61]. With AD initiation, the expression levels of these genes were downregulated and mitochondrial biosynthesis decreased conspicuously [61]. This suggests that disruption and regula-

tion of mitochondrial biosynthesis may be a target for AD treatment. Moreover, PGC-1 α and PINK1 can decrease the peroxidation of mitochondrial fatty acids and have been found to be significantly reduced in the hippocampus of AD patients and diabetic mice [62]. These data indicate that PGC-1 α and PINK1 are essential factors in the modulation of mitochondrial function in the brain, which might be an underlying mechanism in diabetic patients' vulnerability to AD.

As a destructive factor, oxidative stress occurs when cellular metabolic activity is greater than antioxidant capacity or when the amount of free radicals (including ROS and RNS) production/accumulation is too large to be removed. The levels of ROS and RNS were obviously elevated in patients of DM and AD [53, 63, 64], indicating that oxidative stress may be a connection between both diseases. Oxidized proteins/lipids are increased in the brain of AD patients, and there is also evidence that oxidative damage can occur in the early stages of patients with moderate cognitive impairment [58, 65, 66]. Impairment of the respiratory chain, which is associated with oxidative stress and malfunctioning mitochondria, is a typical characteristic of streptozotocin (STZ-) treated rat brains [67]. In line with this, respiration/oxygen consumption is decreased in the brain mitochondria of male STZ diabetic rats [68]. In diabetic rats induced by STZ, thiobarbituric acid reactive species (TBARS) levels were significantly elevated in the hippocampus, while the level of superoxide dismutase (SOD) was markedly downregulated. This was also accompanied by a reduction in mtDNA content and oxidative respiratory chain proteins [54]. Ceretta

et al. also found that diabetic rats had an increased level of superoxide, protein oxidation, and TBARS production in some brain regions, while SOD activity was decreased in the striatum and amygdala [54]. Similarly, the activity of superoxide dismutase, catalase, or glutathione peroxidase is often decreased in diabetic brains [69–72]. The resulting excessive oxidative stress may trigger the discharge of cytochrome C and activate the prodeath apoptotic cascade, which in turn promotes mitochondrial dysregulation [73]. Collectively, these data indicate that oxidative stress arises in the brain and that oxidation products are significantly increased in diabetes models.

Taken together, the above results indicate that the mitochondria in diabetic patients and models represent an imbalance between oxidation and antioxidant capacity. This further exacerbates oxidative stress, disrupts mitochondrial dynamics (fission and fusion) and biological functions, and causes mtDNA mutations. All of these events can result in an insufficient energy supply and reduced antioxidant enzyme activities in the brain area, which eventually increases the risk of cognitive dysfunction and memory defects. In general, DM can aggravate mitochondrial dysfunction and oxidative stress in memory- and cognition-related brain regions, which might be the common underlying mechanism to these diseases.

5. Abnormal Lipid Metabolism: A Key Feature of Neurodegeneration That Is Exacerbated by DM

Lipids are abundant in the brain, particularly glycerophospholipids, sphingolipids, and cholesterol. It has been demonstrated that lipid oxidation products are at high levels in tissues derived from aged mice [74, 75]. In one study of post-mortem AD brains, “adipose inclusions” or “lipid granules” could be found [76]. Physiological and epidemiological investigations have also confirmed that cholesterol metabolism, inflammation, and innate immunity are closely associated with AD [77]. In neurons and other cell types, oligomeric $A\beta$ peptides can alter cellular cholesterol metabolism [78]. This is significant as obesity and dyslipidemia are the main risk factors for T2D, accompanied by increased central adiposity, elevated triglycerides and low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C) [79]. Thus, abnormal lipid metabolism is an overlapping feature of both DM and AD.

Lipids, especially cholesterol, have been discussed at length in the context of neurodegenerative diseases. Disturbance of cholesterol metabolism in the brain is correlated with aging and neurodegenerative diseases such as AD [80]. Cholesterol in the brain is essential for synapse and dendrite formation, as well as axonal guidance [81–83]. However, the BBB can effectively prevent the exchange of substances such as peripheral cholesterol between brain tissue and plasma lipoproteins [84]. Individuals with diabetes often have hyperlipidemia, which can destroy the integrity of the BBB and increase its permeability. As peripheral cholesterol enters into the brain, cholesterol metabolism disorders occur

[83]. In addition, hypercholesterolemia can promote $A\beta$ pathology in the brains of many AD patients and further cause oxidative stress, giving rise to mitochondrial dysfunction and structural damage via lipid peroxidation [85–89]. Increased inflammation has been found in the brains of diabetic mice fed a high-fat diet and may be associated with upregulation of $A\beta$ and phosphorylated tau (p-tau) [85]. In a study performed by Vandal et al., high-fat diets led to glucose intolerance, increased soluble $A\beta$, and memory impairment in 3xTg-AD mice. Strikingly, the authors also found that a single insulin injection reversed the deleterious effects of high-fat diets on memory and soluble $A\beta$ levels, partly through changes in $A\beta$ production and clearance. In addition, the APOE4 allele has been shown to increase the risk of AD in diabetic patients by selectively binding to the $A\beta$ peptide and modulating its aggregation and clearance [90–93]. As such, the results from preclinical assessments and experimental research of AD and DM models support a crucial role for lipid metabolism in the pathogenesis of both diseases.

In addition to cholesterol, fatty acids have been intensively studied in DM and other metabolic diseases, including neurodegenerative diseases. The plasma level of free fatty acids in STZ-induced diabetic rats was significantly higher than that in the control group [89], which is consistent with findings of other diabetic models [94, 95]. However, increased free fatty acids can impair the function of the central nervous system [88]. In addition, AD patients with different levels of memory loss also showed different degrees of metabolic disorders of fatty acids [96]. Consequently, we can conclude that lipid metabolism is a shared link between DM and AD, as well as provides a plausible molecular basis for the pathogenesis, diagnosis, and treatment of diabetic patients who are prone to dementia.

6. Protein Changes in AD and DM

Protein oxidative damage can at least partially explain a wide range of age-related diseases, including metabolic disorders such as DM and obesity, cardiovascular complications such as atherosclerosis, and neurodegenerative disorders such as AD [97]. As a global disease, DM not only is characterized by elevated blood glucose and blood lipid levels but also displays a protein metabolic disorder, which is primarily caused by the absolute or relative deficiency in insulin secretion [98]. Insulin can promote protein synthesis and inhibit protein decomposition [99], and increased insulin and insulin-like growth factor 1 (IGF1) levels in the serum can improve the protein metabolism (Figure 1). Compared with that in a normal group, protein catabolism in diabetic models was significantly ameliorated, while protein synthesis and the mRNA expression of the IR, IGF1, and IGF1 receptor (IGF1R) were markedly decreased [100]. In addition, the branched-chain amino acids (BCAAs), leucine, isoleucine, and their related metabolites were positively associated with insulin resistance.

Protein accumulation in an aggregated form is a common feature of neurodegenerative disorders. These proteins also tend to aggregate in compartments that differ from the compartments where they are localized under physiological

conditions. Over the last decade, many studies have demonstrated that the unfolded protein response (UPR) markers such as binding immunoglobulin protein (BIP), phosphorylated- (p-) protein kinase double-stranded RNA-dependent (PKR)-like the endoplasmic reticulum (ER) kinase (PERK), p-inositol-requiring enzyme (IRE), and eukaryotic initiation factor 2 α (p-eIF2 α) were elevated in the most severely affected tissues of AD patients [101–103]. The most widely studied arm of the UPR response is the PERK-eIF2 α axis. This axis can facilitate A β production and take part in the regulation of synaptic plasticity [104]. UPR and ER stress markers such as nuclear factor- κ B (NF- κ B) target genes, C/EBP homologous protein (CHOP), and immunoglobulin heavy chain (BIP) in inflamed islets of both diabetic mice and patients with autoimmune diabetes were increased [105, 106]. In addition, elevated UPR or ER stress markers are also correlated with tau pathology [107]. In addition to amyloid plaques, neurofibrillary tangles composed of the microtubule-associated protein tau are another hallmark of AD. It has been shown that A β is upstream of tau in the AD pathological cascade [108–111]. In AD, tau is massively phosphorylated, particularly at serine and threonine residues. Generally, hyperphosphorylated tau in the axon detaches from the microtubules and passes through the axon initial segment, which normally acts as a diffusion barrier for physiologically phosphorylated tau, before accumulating in neuronal cell body dendrites. This process is partly mediated by A β [112–114]; however, recently, it was shown that A β could directly trigger endogenous tau overexpression via protein translation and activation of the Fyn/ERK/S6 signaling pathways in the somatodendritic domain [115]. Recent evidence also suggests that AD-related proteins such as A β , islet amyloid polypeptide (IAPP), or tau could promote diabetic phenotypes and further exacerbate neurodegeneration [20].

IAPP or amylin is a key feature of T2D pancreatic pathology [20, 116]. This hormone is secreted with insulin, and its regulation begins with food intake [116]. It has demonstrated that IAPP plays a role in the neurodegenerative process of AD [117, 118], and similar findings in the brains of diabetic patients with AD were observed by Fawver et al. [119]. Colocalization of IAPP and A β in the brain has been observed, and IAPP can alter microvasculature and tissue structures in patients with AD [118, 119]. Thus, IAPP provides further data supporting a connection between AD and T2D. Although there are notable protein changes in both AD and DM, whether these changes directly contribute to the prevalence of AD in diabetic patients requires further exploration.

7. Metabolism and A β Deposition

The common pathological characteristics in DM and AD are the generation of amyloid peptides (APP) and aggregation of abnormal proteins such as elevated serine phosphorylation of IRS-1 levels and activated JNK [33]. Extracellular amyloid plaques consist of insoluble aggregates of A β , which is one initiator of AD. Growing evidence supports the concept that a series of changes caused by DM can increase the risk for A β pathology in many AD cases [120–122]. Due to its positive effects on APP-related gene expression and γ / β secretase,

oxidative stress can promote the pathology of A β [89, 123–125]. In cultured cells, when the concentration of cholesterol ester is increased, there is a proportional elevation in APP [126]. It has been shown that A β deposition can be seen in mitochondria and, correspondingly, that A β deposition can lead to dysfunctional mitochondria such as mitochondrial swelling, mPTPs, and excessive ROS production [127–134]. Therefore, A β has a destructive influence on mitochondrial structure and function. Furthermore, increased levels of A β may be dependent on mitochondrial ROS production, and antioxidant compounds can impede mitochondrial dysfunction and reduce A β generation [73]. Several mechanisms have been proposed to support the idea that insulin signaling dysfunction may lead to A β pathogenesis, which can further impact insulin signaling (Figure 1). This suggests that a self-perpetuating cycle may become established, further exacerbating neurodegeneration [135]. Insulin-degrading enzyme (IDE), a major enzyme responsible for insulin degradation, can also degrade other targets such as glucagon, atrial natriuretic peptide, and the A β peptide and regulate proteasomal degradation and other cellular functions [136, 137]. It has been demonstrated that IAPP can interact with A β and contribute to A β aggregation [138] and conformation [20, 119, 139]. Taken together, a positive feed-forward mechanism may exist between metabolic abnormalities and A β pathology, which may be explained by the overlapping crosstalk between DM and AD.

8. Conclusions and Perspectives

Multiple epidemiological studies have shown an increased risk of AD in many diabetic patients. As there are many shared characteristics between impaired insulin signaling and AD, it is possible that AD is a metabolic disease. Abnormal glucose and lipid metabolism, mitochondrial dysfunction, oxidative stress, and protein changes resulting from DM are associated with impaired insulin signaling pathways. These metabolic factors can increase the prevalence of AD, mostly by promoting A β pathology (Figure 2). Thus, DM is a risk factor for AD that is likely driven by metabolic alterations that exacerbate brain bioenergetic dysregulation. But whether these metabolic factors caused by DM are direct causes or confounders of AD deserves further discussion. Bioinformatics analysis such as Mendelian randomization or genome-wide analysis may help explain the causal relationship between DM and AD. In addition, despite these commonalities, not all DM patients develop AD and not all AD patients are diabetic. In this review, we have explored the overlapping metabolic pathways of DM and AD, which will provide references and suggestions for the underlying mechanisms of diabetic patients with AD. In other words, diabetic patients are more prone to dementia when they have significant metabolic changes such as increased ROS production, abnormal lipid metabolism, and glucose metabolism disorders. In the future, it will be indispensable to clarify whether cognitive decline in diabetic patients can be rescued by adequate metabolic regulation. In addition, it is worth pursuing a comprehensive and integrated analysis of the molecular mechanisms controlling metabolic processes in

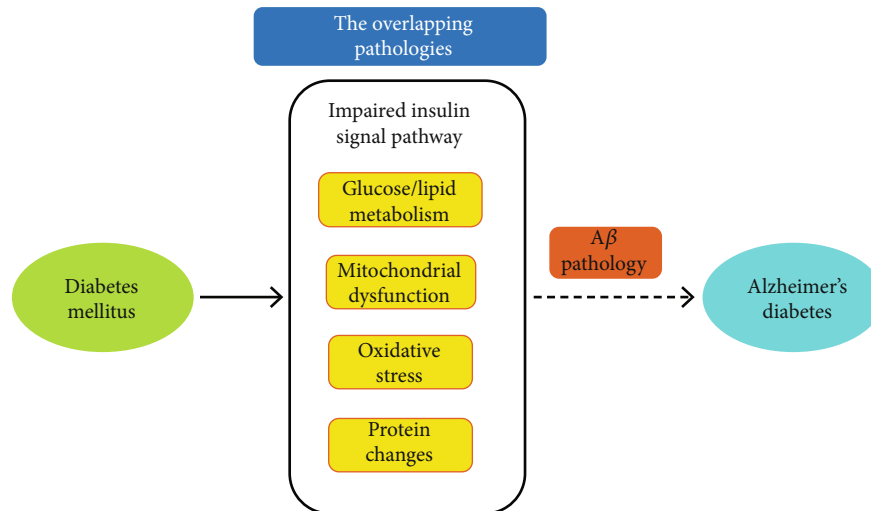


FIGURE 2: The overlapping pathology between diabetes mellitus (DM) and Alzheimer's disease (AD). Due to many shared characteristics with impaired insulin signaling pathways, AD may be a metabolic disease. Metabolic changes including glucose/lipid metabolism, mitochondrial dysfunction, oxidative stress, and protein changes resulting from DM are associated with an impaired insulin signaling pathway. These metabolic factors could increase the prevalence of AD in diabetic patients, mainly by promoting A β pathology.

developing and mature neurons, in order to develop novel therapeutic approaches tailored to the nervous systems of aged people. Furthermore, the crosstalk between these distinct but interdependent biological processes is constantly tuned by shared effectors and regulators. In conclusion, this review discusses the overlapping pathologies between DM and AD from the perspective of metabolism and may accelerate the discovery of new treatments and improve the understanding of DM and AD pathogenesis and progression. Finally, this review may provide theoretical support and new targets for the prevention and treatment of AD in diabetic patients.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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