Review

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Abstract

Epidemiological and clinical research on neurodegenerative diseases have indicated that metabolic dysregulations increase the risk of developing Alzheimer's Disease (AD). Many metabolic alterations can be grouped within the metabolic syndrome (MetS), defined as the coexistence of three or more risk factors, such as insulin resistance, hyperglycemia, hypertension, central obesity, and dyslipidemia. These changes induce a systemic change that plays a critical role in inducing neuroinflammation and neurodegeneration as essential causes of AD pathogenesis. All these factors compromise peripheral tissues and brain energy metabolism through reduced glucose utilization, which contributes to alterations in O-GlcNAcylation, glycosylation, mitochondrial dysfunction, oxidative stress, chronic inflammation, synaptic dysfunction, impaired autophagy, and blood-brain barrier (BBB) dysfunction. However, these factors are modifiable elements that depend on lifestyle. A relatively new perspective proposes that exercise regularly plays an essential role in maintaining brain metabolism in ageing. Physical activity in MetS decreases the risk of developing Alzheimer's disease, is associated with better prognosis, and positively affects cognitive function in those patients. In this review, we discuss the mechanisms involved in MetS and their implication in AD and identify potential areas for preventive and therapeutic interventions.

Keywords: alzheimer's disease; metabolic syndrome; obesity; hyperglycemia; insulin resistance; therapeutic; physical activity

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1. Introduction

In recent decades, the aging of the world population has become a public health problem due to the various chronic degenerative diseases they face. One of the neurodegenerative diseases most closely related to aging is Alzheimer's disease (AD), which accounts for more than 80% of dementia patients worldwide [1]. AD is a progressive and irreversible neurodegenerative disease characterized by cognitive impairment with other symptoms becoming more severe as the disease evolves, ultimately culminating in impaired expressive speech and loss of executive functions. Two AD classifications have been described that share many similarities including clinical, biomarker, and pathological outcomes: 1) Early-onset familial AD, which is associated with mutations in the genes encoding Amyloid Precursor Protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Most people with mutations in these genes develop symptoms before 65 years of age, with an incidence of 5% of the total reported cases for AD. 2) Late-onset AD occurs after the age of 65 and represents 95% of the total reported cases, and age is the most critical risk factor [2].

Epidemiological and clinical studies have indicated that the risk of AD is increased in patients with other comorbidities such as obesity, peripheral hyperinsulinemia, insulin resistance, diabetes, hypertension, and cardiovascular disease [3–5]. These factors together are denominated as "metabolic syndrome" (MetS) and are modifiable elements that depend on lifestyle. All these MetS components induce a systemic change that plays a critical role in inducing neurodegeneration and neuroinflammation, as essential features of AD pathogenesis [6]. The aim of this review is to highlight key issues related to the metabolic dysfunctions that contribute to the development of AD, and to identify potential areas for preventive and/or therapeutic interventions.

2. Alzheimer's Disease and Its Relationship with Metabolic Syndrome

In recent decades, MetS has been relevant because of the new generations changes in lifestyle, which includes an increase in caloric intake that exceeds energy expenditure [6,7]. The global incidence of MetS increases with age, involving around 20% of men and 16% of women under 40 years of age; 41% of men and 37% of women between 40 - 59 years; and 52% of men and 54% of women older than 60 years [8–10]. MetS is a cluster of metabolic dysregulations that include central obesity, insulin resistance (IR), hyperglycemia, hypertension, and atherogenic dyslipidemia [11]. Furthermore, other factors related to MetS include chronic inflammation, endothelial dysfunction, genetic predisposition, hypercoagulability, and chronic stress [8,12,13]. The diagnosis of MetS has been made by scientific societies through worldwide criteria (Table 1), among all of which we highlight those proposed by the World Health Organization (WHO), the International Diabetes Federation (IDF), the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII), the American Herat Association (AHA), the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [14]. All other definitions of SMet are very similar, however the indicated parameters may vary in some units. The presence of three of the five major risk factors is sufficient to confirm a diagnosis of MetS [6].

Table 1. Diagnostic criteria for metabolic syndrome.

Criteria / Clinical Measure	WHO (1998)	NCEP-ATPIII (2001)	IDF (2005)	AHA/NHLBI (2009)
Central Obesity	Waist/hip ration Men: >0.9 Women: >0.85 BMI > 30 Kg/m^2	Waist Circumference Men: >40'' Women: >35''	Waist Circumference Men: >37'' Women: >32''	Waist Circumference Men: >40'' Women: >35''
Blood Glucose	Fasting glucose (≥110 mg/dL)	Diagnosis of type 2 diabetes Fasting glucose (≥110 mg/dL)		

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	Post-load glucose at 2 h (≥140 mg/dL and 200 mg/dL) Glucose intolerance Insulin resistance		Glucose intolerance Insulin resistance	
High triglycerides			≥150 mg/dL	
Low HDL	<35 mg/dL in men <39 mg/dL in women		Men: <40 mg/dL Women: <50 mg/dL	
High Blood Pressure	≥140/90 mmHg		≥130/85 mmHg	
Diagnosis	≥3 criteria one of which should be insulin resistance	≥3 criteria	≥3 criteria one of which should be central obesity	≥3 criteria

The criteria for the diagnosis of metabolic syndrome were established by the World Health Organization (WHO) in 1998, National Cholesterol Education Program-Adult treatment Panel III (NCEP-ATPIII) in 2001. Similar criteria were update in 2006 by the International Diabetes Federation (IDF) and American Herat Association (AHA) in 2009. You may have metabolic syndrome if you have three or more of the conditions listed. BMI: body mass index; HDL-Cholesterol: High-density lipoproteins.

Recently, the increasing prevalence of MetS has been associated with a rise in AD cases. The variety of comorbidities and risk factors an individual may encounter throughout life can elevate the risk of AD, either additively or synergistically (Figure 1) [15–17]. AD is preceded by several decades of metabolic and cellular changes caused by MetS [18]. These changes are associated with a breakdown of brain energy metabolism through reduced glucose utilization, which contributes to alterations in O-GlcNAcylation, glycosylation, mitochondrial dysfunction, oxidative stress, chronic inflammation, synaptic dysfunction, impaired autophagy and dysfunction of the blood-brain barrier (BBB) [19–21].

Metabolic syndrome is defined as the coexistence of obesity, hypertension, hyperlipidemia, and diabetes. Specifically, hypertension alters the vascular walls causing hypoperfusion, ischemia, and cerebral hypoxia, contributing to development of AD. Hyperlipidemia compromises the integrity of the BBB, increases Aβ peptide deposition, promotes Tau hyperphosphorylation, and induces neuroinflammation consistent with AD. The implication of obesity as a risk factor for the development of AD is still under debate. However, some studies have shown that obesity in midlife is a risk factor for dementia. Suggested mechanisms underlying the association between T2DM and AD include insulin resistance, and insulin receptor impairment, among others.

The pathophysiology of AD is characterized by the presence of two histopathological markers that can be observed by microscopy: 1) extracellular neuritic plaques (NPs) formed by the aggregation of amyloid-β (Aβ) peptide; 2) the formation of neurofibrillary tangles (NFTs) that are the product of hyperphosphorylation and aggregation of the Tau protein (Figure 2) [22,23]. The aggregation of NPs and NFTs occurs mainly in the entorhinal cortex, hippocampus, temporal lobe, frontal cortex, and certain subcortical areas, brain structures closely related to learning and memory [1,2,24].

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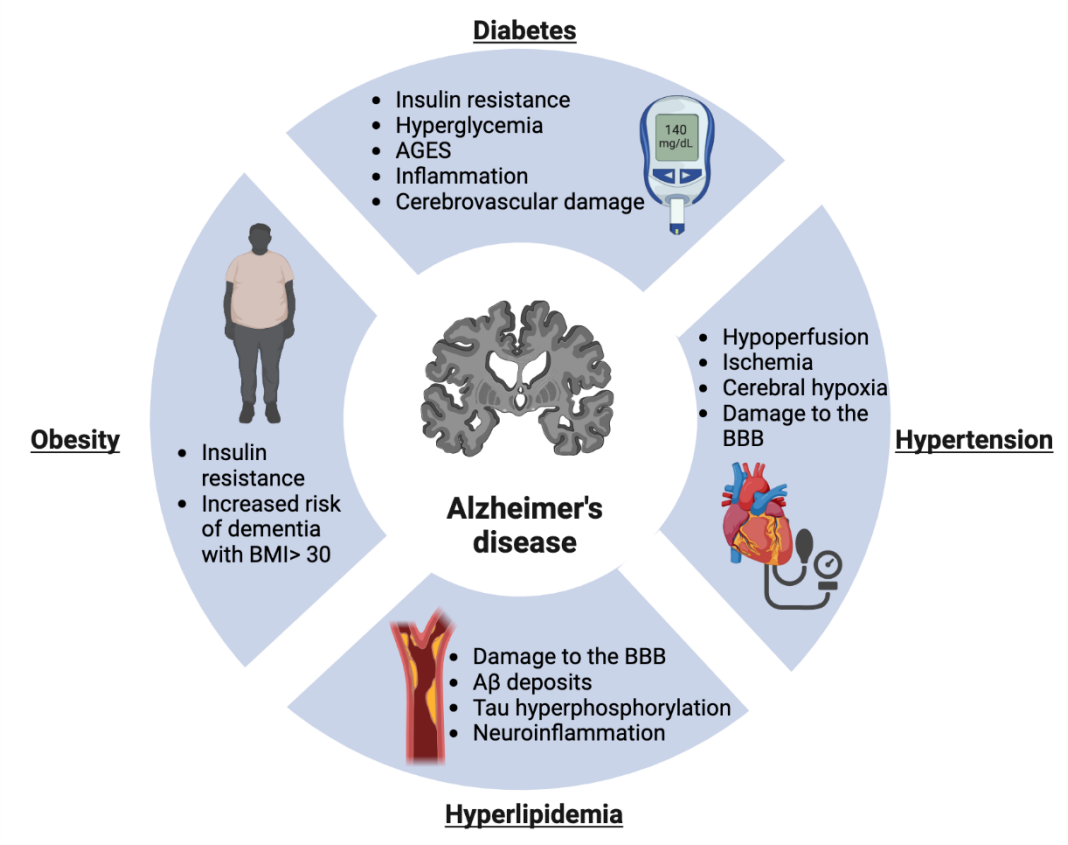

Figure 1. Metabolic syndrome as a risk factor for the development of AD.

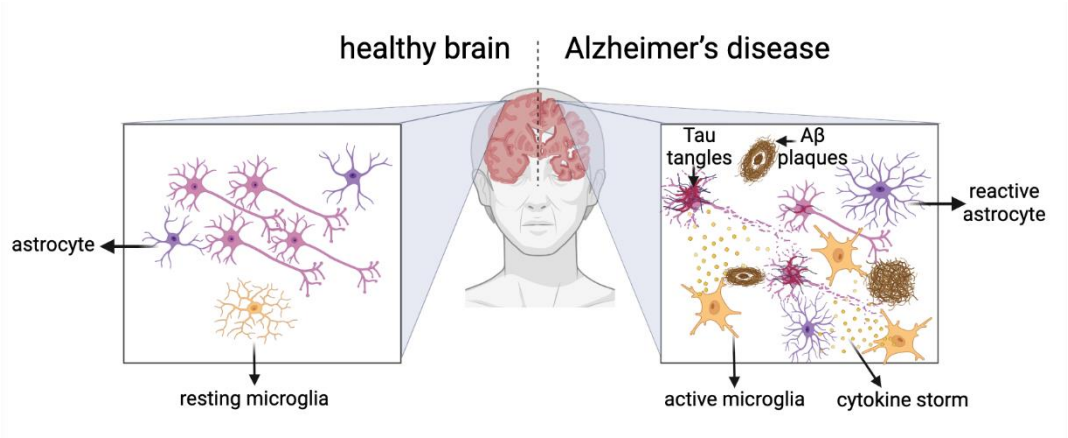

Figure 2. Histopathological markers in Alzheimer's disease, central mechanisms of damage, and their associated biomarkers.

In the brain of a patient with AD, main pathological hallmarks are neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are formed by the aggregation of hyperphosphorylated tau protein, and neuritic plaques are characterized by the aggregation of the Aβ1-42 peptide. It has been found that all other causes, such as pathology and/or neuroinflammation, ultimately converge to Aβ accumulation. For instance, microglia mediate neuroinflammation by the production of cytokines such as IL-1β, IL-6, TNF-α and IL-33. The cytokines produced help in Aβ clearance, whereas IL-8 and IL-1β cause synaptic dysfunction. This molecular mechanism is only part of the complexity of neurodegeneration.

NPs are formed by a heterogeneous combination of Aβ peptides ranging from 20 to 43 amino acids, however, those of 40 to 42 amino acids are the most abundant extracellular deposits. The Aβ

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peptide is produced through the sequential cleavage of APP by the enzymes β-secretase and γ-secretase; this synthetic route is known as the amyloidogenic pathway (Figure 3). However, the cleavage of APP by α-secretase prevents the generation of Aβ because the cleavage site is within the Aβ domain and is called the non-amyloidogenic pathway [25,26]. The Aβ that is obtained by the amyloidogenic metabolism of APP gives rise to fragments that change from α-helical to β-folded conformation. Aβ monomers in the β-folded conformation interacts with other monomers to form oligomers, which, in turn, form fibrils and subsequently insoluble plaques that can be localized intracellularly and extracellularly. Deposits of the Aβ peptide of 40 to 42 amino acid residues form an insoluble fibrillar structure, which is associated with neuronal degeneration [23].

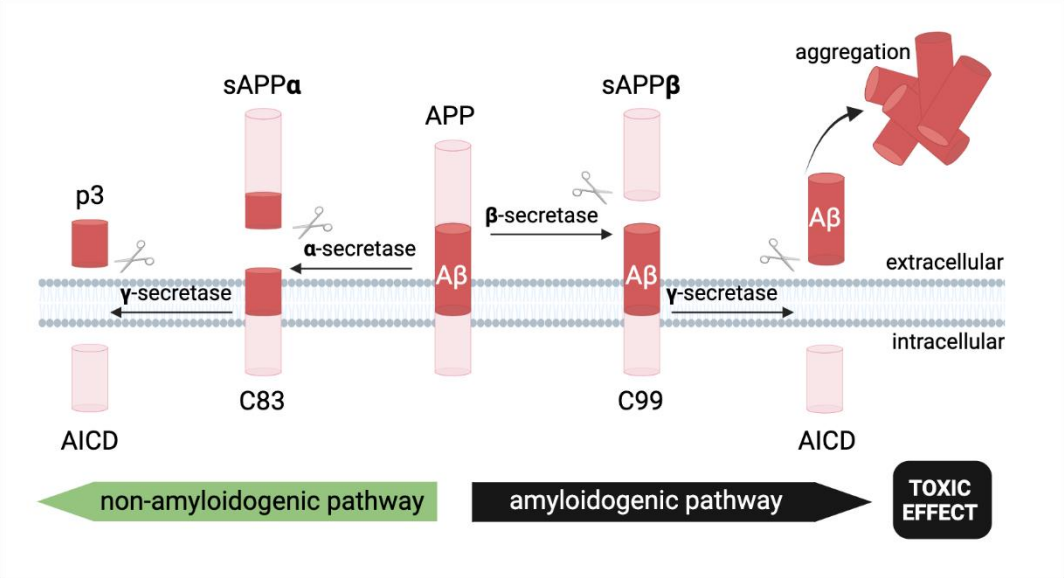

Figure 3. Schematic representation of the APP metabolism.

In the non-amyloidogenic pathway, APP is processed by proteolytic cleavage of α-secretase in the Aβ domain, forming sAPPα and a membrane-bound C-terminal fragment. In the amyloidogenic pathway, APP is sequentially subjected to proteolytic cleavage by β- and γ-secretase to form the soluble peptide Aβ.

Recent evidence suggests that sAPPα peptides produced by the non-amyloidogenic pathway have protective effects on metabolic regulation and could enhance membrane glutamate and glucose transporter activities in neurons, with positive outcomes in synaptogenesis, neurite extension and stimulation of neural progenitor proliferation [1]. However, sAPPβ peptides produced by the amyloidogenic pathway have been associated with metabolic diseases, such as obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, and cardiovascular disease. On the other hand, the accumulation of full-length APP results in mitochondrial dysfunction and decreased energy metabolism, which is detectable in the brains of AD patients. In addition, in peripheral tissues, the mitochondrial localization of APP in adipocytes could greatly damage the function of mitochondria and promote the occurrence of obesity in mice, making a link between obesity and AD [27,28].

In the brains of AD patients, the Tau protein is abnormally hyperphosphorylated, facilitating the formation of insoluble filaments that accumulate as NFTs (Figure 4) [24]. Moreover, the spread of Tau aggregates correlates with cognitive decline and hence with the state of the disease [29]. Tau protein function is regulated by post-translational modifications (PTMs), including phosphorylation, dephosphorylation, acetylation, ubiquitination, methylation, SUMOylation, glycation, glycosylation, O-GlcNAcylation, nitration, oxidation, and truncation (proteolytic cleavage) at serine, threonine, and tyrosine residues [30–32]. Metabolic dysregulations induce variations in the regulation of PTMs of Tau that may cause changes in protein properties and loss of protein functions.

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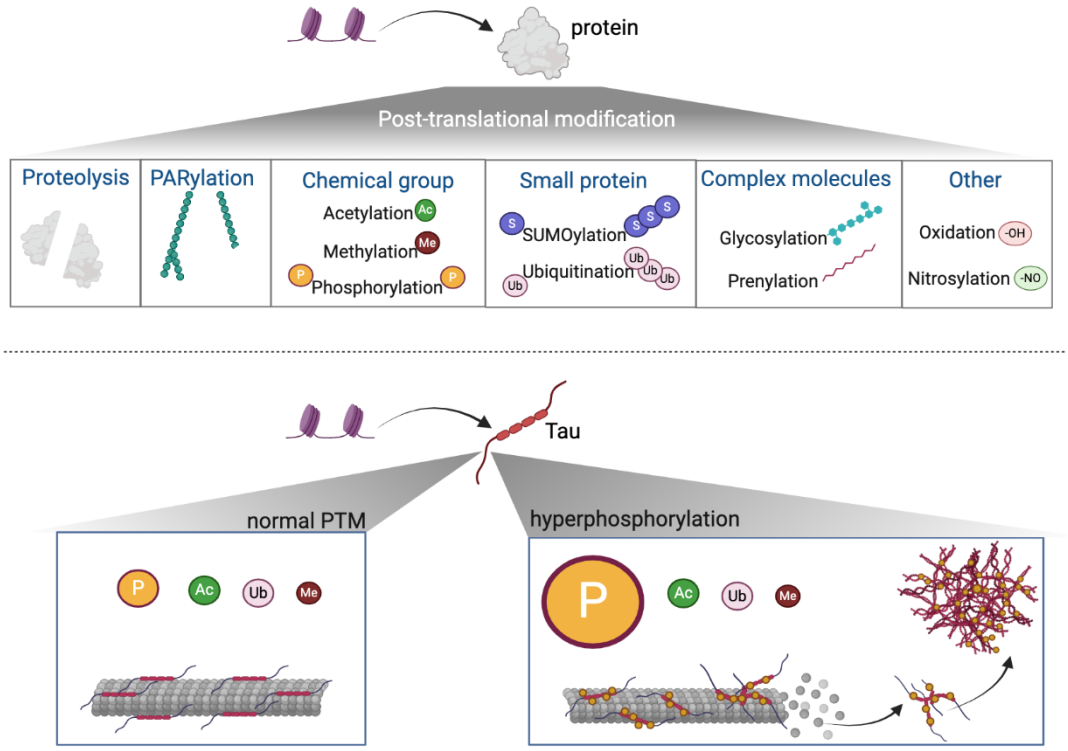

Figure 4. Post-translational modifications in Tau and association with neurodegenerative diseases.

Schematic representation of post-translational modifications of Tau and their impacts on tau function, degradation, and aggregation. Post-translational modifications could result in changes in tau conformations or tau-protein interactions, which promote or suppress Tau phase separation, aggregation, microtubule assembly, and degradation.

In AD brains, Tau from the frontal and parietal cortex showed modifications at 43-55 different phosphorylation sites, 19 acetylation sites, 14-17 ubiquitination sites, and 4 methylation sites [29,32,33]. The tendency for phosphorylation at T^{231}, S^{235}, and S^{262} seems to correlate with clinical progression of AD, as well as correlating with the potential to induce local Tau accumulation in HEK cells [34]. In nonpathological conditions, phosphorylation of Tau relies on the interplay of Tau kinases (GSK-3β, CdK5, PKA, MARK, Fyn, and others) and phosphatases (mainly PP2A); however, hyperphosphorylation of Tau is associated with a dysfunction of these enzymes [35–37]. In the study models of AD in transgenic mice, the mechanisms of Aβ peptide toxicity, impaired glucose metabolism, and inflammation have been suggested to contribute to abnormal Tau hyperphosphorylation [31,35]. This background raises some questions: Are metabolic dysfunctions directly connected to amyloid and Tau pathology? What are the interactions between these pathological events?

3. Impact of Insulin Resistance and Diabetes Mellitus on Alzheimer's Disease

Insulin plays a crucial role in glucose homeostasis, regulating the balance between glucose production by the liver and glucose uptake by muscle and other tissues [38]. However, Insulin resistance refers to the condition where Insulin-dependent tissues do not respond efficiently to physiological Insulin concentrations [39,40]. That is a hallmark of MetS, with detrimental effects on both the periphery and central nervous system (CNS). Brain Insulin resistance leads to reduced neurogenesis, neuronal plasticity, and cognitive decline by promoting neurodegeneration, alterations in dendritic spine density, and changes in neurotransmission. This is observed in various diseases

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such as obesity, diabetes, and AD. In the resistance state, altered Insulin-evoked activity is present in the hypothalamus, cortex, hippocampus, amygdala, cerebellum, striatum, and midbrain [18,41].

T2DM patients often have hyperinsulinemia and low Insulin sensitivity, and epidemiology-based findings have also shown a correlation between T2DM and the risk of developing AD [18,42]. Suggested mechanisms underlying this association include Insulin deficiency, Insulin resistance, impairment of the Insulin receptor, hyperglycemia-induced toxicity associated with adverse effects by advanced glycation product (AGE), inflammation, and cerebrovascular damage. Moreover, it has been shown that carrying mutations in the apolipoprotein E4 (ApoE4) allele and having T2DM increase the risk of developing AD fivefold [3,18,19]. However, antidiabetic drugs have demonstrated some positive effects in the treatment of AD [41,43], and enhancement in the Insulin signaling pathway can promote mitochondrial biogenesis to improve cognition in neuronal disorders associated with T2DM [38,40].

Post-mortem brains from patients with AD display decreased Insulin receptor expression, and disrupted intracellular insulin receptor signaling has been associated with poor cognitive performance [15,44]. Additionally, the absence of insulin increases neuronal susceptibility to metabolic stress, leading to faster neuronal dysfunction [44–46]. The brain regions with the highest Insulin receptor densities are the hippocampus, frontal cortex, and temporal lobe, which are the main areas of neurodegeneration in AD [45]. The Insulin signaling pathways are essential for maintaining phosphorylation homeostasis, and your alterations promotes hyperphosphorylation of Tau in the brains of patients with AD and T2DM [47–49].

4. O-GlcNAcylation, Insulin Resistance, and Tau Hyperphosphorylation

O-GlcNAcylation (*O*-GlcNAc) is a dynamic form of protein glycosylation that involves the addition of the monosaccharide *N*-acetylglucosamine (GlcNAc) to Serine or Threonine residues in nuclear, cytoplasmic, mitochondrial, and transmembrane proteins. The enzymes responsible for this modification are *O*-GlcNAc transferase (OGT) and *O*-GlcNAcase (OGA), whose expression and activity depend on Glucose availability and metabolism through the hexosamine biosynthesis pathway [50,51]. Approximately 2 to 5% of all Glucose entering the cell is channeled into the hexosamine biosynthesis pathway to generate UDP-GlcNAc, making it a pathway sensitive to nutritional modifications [52,53]. However, the relative flux of Glucose to hexosamine biosynthesis pathway in highly metabolic tissues, such as the brain, and the changes generated in the MetS are unknown [54,55]. Under physiological conditions, glutamine:fructose-6-phosphate amidotransferase (GFAT) is the enzyme that converts fructose-6-phosphate to glucosamine-6-phosphate and is therefore, a very important enzyme in the hexosamine biosynthesis pathway. *O*-GlcNAc performs critical functions at the cellular level, so changes in UDP-GlcNAc levels or MetS conditions may affect their function. Thus, it is suggested that *O*-GlcNAc is a unique metabolic signaling mechanism that allows cells to detect and respond to stress, influencing cell survival [50].

One of the most important features in MetS is Insulin resistance, which causes alterations in Glucose metabolism, in *O*-GlcNAcylation, and Tau function. Like phosphorylation, *O*-GlcNAcylation is a dynamic PTM that is affected by the availability of circulating nutrients, especially Glucose. Therefore, excess energy accumulation has been associated with obesity and Insulin resistance, which can lead to dysregulation of *O*-GlcNAcylation [56–58]. Furthermore, in some proteins, such as the tau protein, *O*-GlcNAcylation could occur at Ser/Thr residues that could be targeted for phosphorylation. Tau has at least 12 potential *O*-GlcNAcylation sites that are mostly inversely correlated with phosphorylation status [31]. In AD, the Tau abnormal phosphorylation by kinases including GSK3β, CDK5, MAPK and MARK, and its dephosphorylation by phosphatases such as PP2A [30,33,35,36] can be modulated by insulin. Thus, impaired Insulin signaling in Insulin resistance initiates aberrant activation of GSK3β with increased phosphorylation and accumulation of hyperphosphorylated Tau. Therefore, a precise regulation of PI3K-Akt pathway signaling is critical for the control of amyloid and Tau-hyperphosphorylated neuropathologies in AD [30,36,59]. Recent studies have shown reduced CNS Glucose metabolism and *O*-GlcNAcylation promoting increased Tau phosphorylation

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in vivo and *in vitro* models. However, the increase in *O*-GlcNAcylation decreases the pathological accumulation of Tau. Thus, failure of proper Insulin signaling can promote hyperphosphorylated Tau accumulation with NFTs formation and disrupt cytoskeletal function in neural networks and axonal transport, contributing to loss of synaptic connections and progressive neurodegeneration [60–64].

5. Obesity as a Risk Factor in Alzheimer's Disease

Obesity is caused by excessive body fat accumulation [47,65]. Accumulation of perivascular adipose tissue promotes vascular changes and decreases blood flow to the brain, leading to injury by ischemia [66–68]. It leads to chronic low-grade systemic inflammation, leading to increased oxidative stress that can contribute to the development of neurodegeneration [69–71]. The brain areas vulnerable to ischemia are the hippocampal CA1 and CA3, caudate nucleus, layers III, V, and VI of the cortex, and cerebellum [72,73]. Due to its high baseline metabolic activity, the hippocampal area is extremely susceptible to reduced oxygen and glucose intake, and it is believed that this can be one of the causes of increased memory loss [74,75]. In addition, obesity is established as a risk factor that increases the probability of developing AD and other dementias; accordingly, it has been linked to cognitive deficits due to impaired long-term potentiation, synaptic plasticity, and smaller brain volume [76–78].

In white adipose tissue, adipocytes actively release adipokines, including Leptin, Adiponectin, interleukins, Plasminogen activator inhibitor 1 (PAI1), Adipsin (complement factor D), and growth factors [77,79,80]. Leptin increases with food consumption, which tends to reduce eating behaviour. However, in obesity, Leptin levels are increased, and there is no signaling of satiety due to peripheral and central resistance to Leptin signaling. Thus, the disruption of Leptin signals could contribute to AD development [27,81,82]. Leptin is overexpressed in the adipose tissue of individuals with obesity and acts on the CNS, specifically on the hypothalamus, the cerebral cortex, and the hippocampus [82,83]. These regions are among the first regions affected by cognitive deficit in AD and express the long form of the Leptin receptor (LepRb), which is the only Leptin receptor capable of transmitting complete Leptin signaling [83–85].

Recently, the gut microbiome and the state of the CNS have become relevant to obesity. The composition of gut microbiota is influenced by diets high in fats and sugars, which can alter the gut-brain axis and consequently have complex effects on AD susceptibility [86,87]. A change in the gut microbiome (or dysbiosis) due to diet can lead to neurodegeneration through various mechanisms regulating peripheral neurotransmitters, metabolites, and immune signaling molecules [88,89]. Recent studies have shown that the diversity of gut microbiota in AD patients was significantly reduced. At the phylum level, these studies revealed that the microbiome of AD participants shows decreased in *Firmicutes* and an increase in *Bacteroidetes*, which correlates with a decline in cognitive abilities [90,91]. This dysbiosis causes an increase in inflammatory signaling across the gut-brain axis, conveying the host's health status and triggering a regulatory response that aims to restore homeostasis or, depending on the context, escalates inflammation. Furthermore, recent research suggests that administering prebiotics and probiotics can help restore this dysbiosis, allowing a return to a proper homeostatic balance, which could reduce the risk to developing AD [89,92].

6. Dyslipidemia

Dyslipidemia is classically characterized by high triglyceride (TG) serum levels, low HDL cholesterol, and elevated low-density lipoprotein (LDL) cholesterol [93]. One of the main abnormalities driving dyslipidemia is insulin resistance, which aggravates other disorders, particularly hypertriglyceridemia [94]. Elevated levels of cholesterol, especially LDL cholesterol, are a well-known risk factor for developing coronary artery disease and stroke. Additionally, human epidemiological studies have indicated that high serum total cholesterol level is associated with an

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increased risk of developing AD. This gives rise to the idea that treatment for hyperlipidemias, such as statins, may be beneficial in preventing AD [95,96].

Genetic studies on AD have identified single-nucleotide polymorphisms (SNPs) in several genes involved in cholesterol metabolism or transport, including Apolipoprotein E (*APOE*), Apolipoprotein J (*APOJ*, *CLU*), ATP-binding cassette subfamily A member 7 (*ABCA7*), and Sortilin-related receptor (*SORL1*) [96,97]. The *APOE* gene has 3 common variants, $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. The presence of specific polymorphisms in one of the two ε4 alleles increases the risk factor by 12 to 15 times and reduces the age of onset of AD by about 15 years. Moreover, the APOE$\varepsilon 4$ allele is associated with higher plasma total and LDL cholesterol concentrations and promotes fibril formation from soluble Aβ [98]. Genetic variation in the *SORL1* gene, also known as LR11, contributes to AD through various pathways. It is a central regulator of the trafficking and processing of APP, involved in Aβ destruction, and interacts with ApoE and Tau protein [96,99]. The clusterin gene (CLU; also known as APOJ) is involved in reverse cholesterol transport as a constituent of HDL particles and acts in aggregation of Aβ peptides, thereby promoting amyloid plaque formation. Moreover, it may be involved in the transport of Aβ across the BBB and in its uptake by glial cells and brain macrophages [100].

Elevated cholesterol levels impair the function and structure of the BBB, thereby raising the risk of AD [95,101,102]. The imbalance of lipid levels increases the conversion of systemic cholesterol into 27-hydroxycholesterol, which may cross the BBB and promote the deposition of the Aβ peptides and Tau protein characteristic of AD [103]. Moreover, it has been demonstrated that cholesterol can enhance the activity of the β- or γ-secretase enzymes in the amyloidogenic pathway, thereby promoting the production of the Aβ peptide from APP and reducing the non-amyloidogenic α-secretase pathway. Consequently, it promotes Aβ peptide accumulation and influences several non-amyloid factors, such as Tau hyperphosphorylation, neuroinflammation, cognitive impairment, and dysfunction of cholinergic neurons, which align with the development of AD [28,104,105].

Moreover, observational studies have suggested that statins, the group of drugs widely used to lower blood cholesterol, can decrease the incidence of AD or even improved disease progression [95,105,106]. However, clinical studies have not demonstrated the statins efficacy against the onset and/or progression of AD at various stages of the disease. Furthermore, persistently high levels of free fatty acids have been shown to cause harmful effects, including low-grade inflammation that could result in insulin resistance [106,107]. Although the ability of fatty acids to pass through the BBB is limited, Positron Emission Tomography (PET) studies have demonstrated the uptake of fatty acids by the brain. Accordingly, MetS causes the uptake and build-up of fatty acids in the brain, and this can be reversed through weight reduction [108]. Furthermore, research has shown that exposure to a high-fat diet promotes the pathogenesis of AD, and diets enriched in polyunsaturated fatty acids, such as docosahexaenoic acid, show a protective effect against AD [109]. Thus, saturated fatty acids could promote the cerebral inflammatory response by activating the Toll-like receptor-4 (TLR4). Indeed, TLR4 loss of function protects against deleterious effects induced by a high-fat diet [110,111]. Furthermore, the molecular link between high levels of fatty acids and AD could be Aβ and Tau, as free fatty acids have been shown to stimulate the assembly of Aβ and Tau filaments *in vitro*, leading to cognitive dysfunction [105,106].

7. Inflammation

MetS can induce cellular stress, leading to inflammation mediated by cytokines, chemokines, and both innate and long-term adaptive immunity cells. Inflammation caused by overnutrition, known as metabolic inflammation, has been shown to affect the CNS, especially the hypothalamus. It commonly underpins the development of various MetS components such as obesity, Insulin resistance, atherosclerosis, and hypertension [112,113]. These proinflammatory events cause prolonged activation of microglia in the brain and sustained expression of the transcription factor NF-κB, which enhances the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, contributing to a dysregulated immune response and ultimately leading to neurodegeneration. Moreover, the NF-κB signaling pathway may use parallel mechanisms that cause imbalance in

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Glucose homeostasis, driven by impaired Insulin secretion, Insulin resistance, and Glucose intolerance [114].

As previously mentioned, one of the first regions to experience the adverse effects of inflammation is the hypothalamus. The hypothalamus is a crucial control center for energy and weight balance, and its dysfunction contributes to the development of obesity [115,116]. A diet rich in saturated fatty acids promotes Leptin and Insulin resistance through the NF-κB pathway, impairing the hypothalamus' ability to reduce hunger and regulate blood Glucose [83,85]. In the long term, it causes changes in body weight due to increased caloric intake, leading to chronic energy imbalance, as well as a reduction in the number of synapses in hypothalamic neurons and an increase in neuronal apoptosis [44,83,84].

In the AD, it has been observed that Aβ peptide aggregates can bind to different pattern recognition receptors (PRRs) expressed on microglia and astrocytes. One of the main receptors is TLR4, which recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), activating the myeloid differentiation primary response protein 88 (MyD88), which in turn activates NF-κB [117,118]. Furthermore, the binding of the Aβ peptide to the CD36 scavenger receptor and TLR4 receptor leads to the overactivation of microglia, causing a sustained inflammatory process with increased production of reactive oxygen species (ROS) [119–121]. ROS resulted from increased aerobic respiration in mitochondria, elevated NADPH oxidase activity in phagocytic cells, and nitric oxide (NO) production by inducible nitric oxide synthase (iNOS) [122]. This supports an important role of the inflammatory cascades in the neurodegenerative process.

Recently, transcriptome analysis has shown that several AD risk genes are expressed in microglia. ApoE and the triggering receptor expressed in myeloid cells 2 (TREM2) have been identified as two of the main genes involved in both microglial activation and AD pathogenesis [121,123]. The TREM2 receptor is required for microglial proliferation, survival, and aggregation, which has been implicated in the phagocytosis of Aβ plaques and dead neurons with damaged myelin [124–127]. TREM2 variants R47H, R62H, and D87N decrease TREM2 binding to ApoE, alter its binding to phospholipids, and increase the risk of sporadic AD. Particularly, the R47H variant of TREM2 increases 2 to 4 times the risk of developing AD, very similar to that reported in patients with a copy of ApoE ε4 [127–129]. Taken together, the above evidence suggests that microglia play a crucial role in susceptibility to metabolic disorders, which contribute to the development of AD, rather than merely being a consequence of the disease response.

8. Hypertension

Brain function and blood pressure are closely interconnected. Although the brain accounts for only a quarter of our body weight, it receives nearly one-fifth of our cardiac output. The cardiac output delivered to the brain is due to its high metabolic needs, which, along with physiological systems, coordinate and maintain blood flow to the brain. It should, therefore, come as no surprise that circulatory disorders significantly affect brain function [102,130]. Therefore, hypertension causes neurovascular dysfunction and damages small arteries, arterioles, and brain capillaries, which can independently or together result in neuronal injury, synaptic dysfunction, and neurodegeneration [131]. When hypertension occurs in middle age, it may contribute to the development of later AD and vascular dementia 15 to 20 years afterwards.

Specifically, hypertension damages the vascular walls, leading to hypoperfusion, ischemia, and cerebral hypoxia [130,132–134]. Endothelial injury caused by hypertension activates astrocytes and microglia, which mediate the inflammatory response and releases vasoactive cytokines and chemokines. Degeneration results in the loss of capillary dilation in response to neuronal stimuli, hypoperfusion, and BBB breakdown, with the accumulation of blood-derived toxins and fluid in the perivascular spaces. Recent evidence indicates that blood vessels damage can trigger a cascade of events leading to Aβ build-up and an increase in NFTs density in the hippocampal formation

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[135,136]. However, lifestyle can modify the effects; for example, moderate exercise and diet have beneficial effects on cardiovascular and cerebrovascular system.

9. AGES and RAGES

When reducing sugars react with amino groups on the side chain of Lysine residues in proteins, several processes produce advanced glycation end-products (AGEs), which can bind to their AGE receptor ligands (RAGEs) in cells [137,138]. AGE formation involves not only the direct reaction of these residues with sugars but also oxidative damage to proteins; the combination of these reactions is often called glycoxidation. Glycoxidation is highly relevant to AD, partly because extracellular fibrillar aggregates of Aβ have characteristics of AGEs and bind to RAGEs in neurons and brain endothelial cells [139,140]. The binding of AGE and Aβ to RAGE leads to increased oxidative stress, which contributes to neuronal death and vascular dementia in AD. Glycation can delay the transformation of Aβ into fibrils, thus prolonging its existence in toxic oligomeric forms. Vascular dysfunction further worsens cognitive deficits in AD [137,140].

10. Physical Activity and Contribution to the Prevention of Metabolic Syndrome and Alzheimer's Disease

The advantages of physical activity are well-recognized and evident in maintaining the body's homeostasis. Lifestyle modifications and exercise are essential for good health, helping to prevent many chronic diseases in modern society [141,142]. Exercise causes long-term adaptations that reduce cardiovascular risk factors, blood pressure, Glucose, Insulin, total Cholesterol, body mass index, and waist circumference. Therefore, physical activity is likely to be a candidate for alleviating various diseases, including metabolic disorders, neurodegenerative conditions, chronic degenerative diseases, many types of cancers, and cardiovascular illnesses [143,144].

Physical activity is classified into two types: 1) Endurance (aerobic) exercise training, which refers to exercise in which glucose metabolism depends on oxygen under aerobic conditions; 2) Resistance (anaerobic) exercise training, which involves weight or overload in anaerobic conditions and a short period of high-intensity or maximal-intensity activity [145,146]. The diversity of exercise triggers different physiological adaptations in the cardiovascular and respiratory systems, and the movement of skeletal muscles determines the body's functional capacity, performance, and health outcomes [145].

Although attention has often been centered on skeletal muscle adaptations to exercise, all organs in the body are affected by exercise in the short and long term. The primary peripheral tissues produce diverse proteins, for instance myokines by skeletal muscle, hepatokines by the liver, and adipokines by adipose tissue. These proteins play roles in regulating energy homeostasis and overall insulin sensitivity. During exercise, some of these proteins, collectively named "exerkines", are secreted and form a complex inter-organ network that contributes to the systemic metabolic health benefits of exercise [147,148]. The bioactive myokines are released from contracting skeletal muscle during exercise, along with numerous cytokines, peptides, and metabolites [149–151]. Myokines may mediate many of the systemic advantages of exercise, such as affecting adipose tissue, the liver, pancreas, heart, blood vessels, and brain, thereby aiding in protection against neurodegeneration.

Cognitive function and brain health are also influenced by exercise, which is especially relevant for healthy ageing. The secretory response of skeletal muscle promotes the release of brain-derived neurotrophic factor (BDNF), leading to the growth of neurons; vascular endothelial growth factor (VEGF), which supports the development of essential blood vessel; and insulin-like growth factor (IGF-1), which is vital for exercise-induced angiogenesis [151,152]. As a result, it is well established that exercise increases angiogenesis and blood flow in the brain [153]. Because brain metabolism depends on oxygen and glucose, increasing capillary networks improves their supply to brain tissue, supporting neuronal plasticity. This enhanced neuronal plasticity involves the formation of new synaptic connections and the growth of neuronal networks. These structural and functional

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adaptations improve learning ability and memory formation, leading to more efficient cognitive function. As we age, maintaining a brain with better neural plasticity or functionality becomes increasingly important. Older adults in good physical health can expect greater cognitive reserves and a slower ageing process. Even when facing cognitive decline, individuals can enhance cognition through exercise as a therapeutic approach [150,153]. Accordingly, exercise has been shown to significantly improve cognition and mood in patients with AD.

All these factors are determinants of long-term brain health, with regular physical activity improving brain function regardless of health status and age. Moreover, exercise promotes improved whole-body fat oxidation and decreased visceral fat. For example, impaired insulin signaling, commonly called insulin resistance, is believed to be a shared hallmark of MetS, with detrimental effects on the periphery and CNS. Brain insulin resistance is related to diseases such as obesity, diabetes, and AD, which are also predominantly associated with altered metabolic function. Insulin acts on neuronal circuits to control systemic metabolism and body weight by activating its receptors expressed in neurons and nonneuronal cells. Disruption of insulin receptors in the brain results in a decrease in neuronal plasticity and cognitive decline. Insulin deficiency promotes neurodegeneration, as it is closely related to maintaining neuronal plasticity, dendritic spine density, and neurotransmission, and even regulates adult neurogenesis. In the resistance state, altered insulin-evoked activity is present in the hypothalamus, cortex, hippocampus, amygdala, cerebellum, striatum, and midbrain. Compromised insulin sensitivity can be restored by exercise by increasing skeletal muscle glucose uptake and improving glycemic control [44,45].

The neural basis of exercise-based therapeutic interventions has been extensively mapped in animal models. Those studies suggest that physical activity or exercise can lead to improved morphological and functional changes in the brains of older animals. Exercise interventions promote changes in the motor cortex, cerebellum, striatum, and hippocampus in rats. Aerobic exercise increases functional connectivity and gray and white matter volumes in the motor, prefrontal and temporal cortices. Although previous studies have suggested the potential of exercise to increase brain plasticity, the underlying functional changes in brain areas that explain the exercise-induced improvement in middle-aged and older adults remain unclear. Protective mechanisms might result from promoting metabolic stress through exercise, resulting in long-term adaptations associated with protection against metabolic and also neurodegenerative diseases. However, the mechanisms through which exercise protects the CNS remain controversial (Figure 5). Therefore, it is suggested that there is a complex relationship between exercise and brain health, depending on the adult life stage [151].

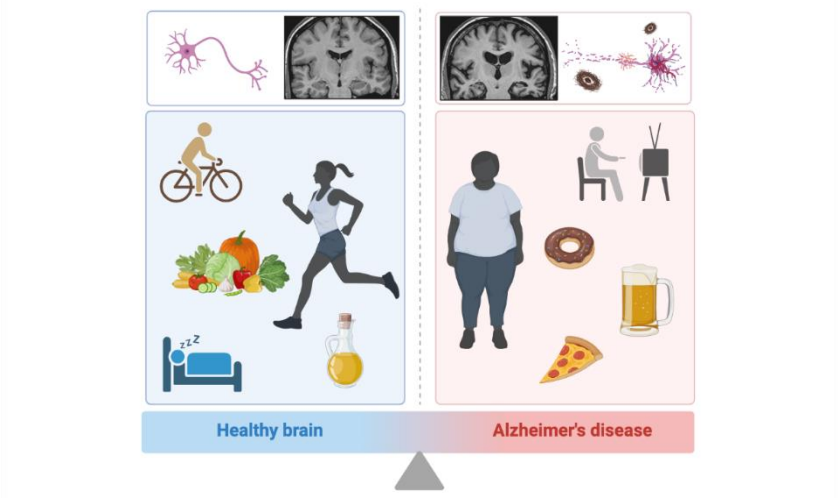

Figure 5. Lifestyle changes contribute to slowdown the development and/or evolution of Alzheimer's disease.

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Several pathways might explain how exercise protects the brain and contributes to slowdown Alzheimer's disease development and/or evolution. In mice, exercise enhances vascular health and increases the amount of neurotrophic factors in the brain, promoting neurogenesis, neuron survival, and new synaptic connections.

11. Exercise as a Therapeutic Strategy in Alzheimer's Disease

Associated with the comorbidities of ageing due to a deficiency in insulin signaling [154], Insulin resistance might synergize with inflammation, oxidative stress, adipose tissue accumulation, excess lipid storage in the liver and muscle, and the loss of lean muscle mass that can occur with ageing to increase the risk of T2DM and fatty liver [155,156]. Physical activity could then be a potential strategy to improve cognitive function, or at least attenuate cognitive decline, in people at risk of AD, and affected patients [143,151]. Therefore, multimodal interventions that include the adoption of an active lifestyle should be recommended for older populations [157,158]. The availability of transgenic mouse models that simulate the main neuropathological characteristics of AD has made it possible to study the main protective mechanisms of exercise on brain ageing. Studies by Choi et al. show that, in a 5xFAD transgenic mouse model of AD, exercise improves memory by stimulating neurogenesis in the hippocampus by increasing levels of brain-derived neurotrophic factor (BDNF). This work is important because it proofs that stimuli promoting BDNF expression and neurogenesis could effectively improve the prevention or the slowdown of AD or participate to decrease its evolution. In the future, it will be important to understand how exercise affects neurogenesis and BDNF levels at the CNS and particularly at the synapse, cellular (neurons, glia, and vascular cells), and circuit levels [159]. Indeed, it is already known that exercise causes the formation of new synapses and is excellent for cardiovascular health, both of which can be relevant for the treatment of MetS and AD [134,143,151,160]. At best, assuming that these results are replicated in other models and are relevant to human disease, this study suggests that we could bottle up the effects of exercise to improve prevention and/or treatment of dementia.

Studies by van Praag et al., 2000 have shown that an "enriched environment" involving the placement of animals in large cages containing running wheels, colorful tunnels, and assorted toys can promote hippocampal neurogenesis and neuronal plasticity [161]. Thus, animals placed in an enriched medium improve memory formation and increase neuronal proliferation, differentiation, and integration in the dentate gyrus of the hippocampus, as well as recovery from a memory deficit induced by injury [162]. Morphologically, exposure to an enriched medium induces an increase in the number of dendritic spines, a greater number of ramifications and synapses formed, which implies that these changes are the result of the context and the level of the stimulus [162,163]. This ties with studies showing that older adults who exercise are more likely to maintain cognition [164]. Physical exercise promotes Aβ turnover, inflammation, neurotrophins synthesis and release, and improve cerebral blood flow, which promote brain protection. A change in lifestyle in the presymptomatic and predementia stages of elderly may have a positive effect on delaying the development of metabolic disorders and dementias [158,165].

In the early stages of AD, there are deficiencies in cognitive functions, usually limited mainly to episodic memory, for which the hippocampus has a crucial role [24,166,167]. However, it is unclear whether the cognitive deficit is due to alterations in the encoding and consolidation of episodic information or impaired retrieval of information stored in memory. In the early stages of AD, changes in synaptic phenotypes have been identified as the main correlates of cognitive deficits in both human patients and mouse models [166]. The Aβ peptide's deposition and the amyloid plaque's formation generate a progressive reduction in the density of dendritic spines in neurons that are part of the engram of memories formed in the hippocampus. Studies carried out in transgenic mice at an early stage of AD, direct optogenetic activation of the neurons that form the memory engram in the hippocampus, results in the recovery of dendritic spines and long-term memory. This demonstrates that although the transgenic mice are amnesic, optogenetic induction of long-term potentiation at engram neuron synapses restores dendritic spine density and long-term memory [168]. Therefore,

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selective salvage of dendritic spines in engram neurons may lead to an effective strategy to treat memory loss in the early stages of AD. One of the benefits of physical activity is that it goes beyond the skeletal muscle and involves adaptations in other organs. In summary, physical exercise promotes positive functional changes in hemodynamic activity, synaptic plasticity, neurogenesis, and proliferation of neural cells with newly formed neurons that are functionally integrated into neuronal networks.

12. Conclusions

In this manuscript, the metabolic alterations in MetS are described, to understand their impact on the development of dementia, especially in AD. Focusing on the mechanisms of obesity, hypertension, dyslipidemia, inflammation, and T2DM. In addition, alternatives are proposed to protect from, or at least slowdown, the development of neurodegenerative disorders. AD is a disease without effective treatment. In this scenario, it is essential to address modifiable risk factors such as obesity, diabetes, hypertension, and dyslipidemia (i.e., metabolic syndrome) to try to prevent or slowdown the onset and progression of AD and improve the quality of life of patients. Accordingly, T2DM has gained central attention in recent decades. However, acting on neuronal insulin signaling has controversial effects on the pathogenesis of AD. Therefore, since no current pharmacological intervention can modify the pathophysiological mechanisms related to the development of this devastating disease, to find an effective treatment, the focus is moving toward other brain cells such as microglia and astrocytes and in the specific population of neuronal cells that predominantly die in the disease. Thus, considering the influence of lifestyle in the crosstalk between all these types of cells, as well the specificity of the biological macromolecules that characterize each of them, will open new avenues in the development of more efficient preventive and therapeutic strategies.

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