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Review Article

A Comprehensive Review of Alzheimer's Disease: Pathophysiology, Diagnosis, and Therapeutic Advances

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most prevalent cause of dementia, predominantly affecting aging populations. It is characterized by memory impairment, cognitive decline, and behavioral disturbances resulting from neuronal loss and synaptic dysfunction. Molecular hallmarks include extracellular amyloid-β (Aβ) plaque deposition, intracellular tau hyperphosphorylation, neuroinflammation, and oxidative stress, which collectively contribute to neural damage and cognitive impairment. Recent advances highlight the importance of early diagnosis through biomarkers such as cerebrospinal fluid Aβ/tau ratios, PET imaging, and emerging blood-based diagnostic tools. Current therapeutic strategies primarily provide symptomatic relief, yet novel disease-modifying approaches targeting Aβ, tau, neuroimmune pathways, and gene-based therapies are under active investigation. Future prospects emphasize personalized medicine, lifestyle-based prevention, and integration of multi-modal biomarkers to enhance early detection and treatment outcomes. This review summarizes updated insights into pathophysiology, diagnostic progress, and evolving therapeutic innovations in Alzheimer's disease.

INTRODUCTION

The cortex and hippocampus parts of the brain are the primary targets of Alzheimer's disease (AD), a progressive and irreversible neurodegenerative illness that gradually impairs memory, cognitive function, and functional independence [1,2]. The German physician and neuropathologist Alois Alzheimer initially reported it in 1906 when he discovered the distinctive neuropathological characteristics of neurofibrillary tangles and amyloid plaques in the brain tissue of a patient suffering from dementia [3]. About 60 to 70 percent of dementia cases globally are AD, making it the most common kind of dementia [4]. The World Health Organization (WHO, 2023) estimates that over 55 million people worldwide suffer from dementia, and that figure is expected

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to rise to 139 million by 2050, primarily as a result of population aging [5].

The strongest recognized risk factor for the condition is age, and it primarily affects older persons. The association between aging and neurodegenerative vulnerability is shown in the prevalence, which doubles almost every five years after the age of 65 [6].

Early-onset Alzheimer's disease (EOAD), which makes up 5–10% of all cases of AD and is frequently linked to genetic mutations in the amyloid precursor protein (APP), presenilin-1 (PSEN1), or presenilin-2 (PSEN2) genes, occurs in a smaller subset of patients, usually before the age of 65 [7, 8]. When Alzheimer's disease is diagnosed clinically, it starts with mild memory loss and trouble acquiring new information and develops over years into language impairment, confusion, personality changes, and loss of thinking and judgment [9]. Patients reach advanced phases where they are totally reliant on caretakers to perform everyday tasks [10]. Families and healthcare systems around the world bear a heavy emotional, social, and financial cost as a result of the disease's delayed onset and chronic course [11].

2. EPIDEMIOLOGY

About 60–70% of dementia cases globally are caused by Alzheimer's disease (AD), making it the most common cause of dementia [12]. The World Health Organization (WHO, 2023) estimates that there are currently 55 million dementia sufferers worldwide, with about 10 million new cases reported each [13]. Alzheimer's disease is the primary cause of disability and reliance among older adults, accounting for the majority of these [14]. After age 65, the prevalence of AD doubles roughly every five years, increasing exponentially with age [15]. Approximately 5–8% of those over 60 have dementia, according to population-based studies, and this percentage jumps Given rising life expectancy and population aging, the worldwide burden of Alzheimer's disease is predicted to increase significantly over the next several decades. According to projections, there will be 139 million dementia sufferers by 2050, with the biggest increases taking place in low- and middle-income nations with underdeveloped healthcare systems [13,17]. Global economy, caregivers, and public health systems face significant problems as a result of this demographic shift [18].

Given rising life expectancy and population aging, the worldwide burden of Alzheimer's disease is predicted to increase significantly over the next several decades. According to projections, there will be 139 million dementia sufferers by 2050, with the biggest increases taking place in low- and middle-income nations with underdeveloped healthcare systems [13,17]. Global economy, caregivers, and public health systems face significant problems as a result of this demographic shift [18]. Regional differences are also evident in epidemiological data. Due to better diagnosis and longer life expectancies, North America and Western Europe have the highest frequency [19]. However, due to their rapidly growing older populations, Asia, Africa, and Latin America are expected to see the largest growth in new cases [20].

Women are more prone than men to develop Alzheimer's disease, in part because they live longer and may be influenced by hormonal variables including the drop in estrogen after menopause [21]. Furthermore, AD's incidence and mortality rates are still rising worldwide, underscoring the critical need for early detection initiatives and preventative measures [22].

3. ETIOLOGY AND RISK

Factors Alzheimer's disease (AD) has a complicated etiology that includes age, metabolic and vascular variables, genetic susceptibility, and environmental impacts. These factors all work together to cause progressive neurodegeneration [23].

3.1 The main risk factor is age.

The most important and reliable risk factor for Alzheimer's disease is growing older. After the age of 65, the prevalence of AD doubles roughly every five years, and almost one-third of people over 85 have dementia of some kind [24]. Neurons are more susceptible to tau pathology and amyloid-β toxicity due to age-related physiologic changes, including as oxidative stress, mitochondrial dysfunction, poor autophagy, and decreased synaptic plasticity [25]. Neuronal damage and cognitive decline are also influenced by age-related vascular dysfunction and persistent low-grade inflammation, or "inflammaging" [26].

3.2 Genetic Variables

Particularly in cases of familial or early-onset Alzheimer's disease (EOAD), genetic predisposition is important. Autosomal dominant types of AD are caused by mutations in three important genes: amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) [27]. Amyloid-β42, a peptide that is prone to aggregation and plaque formation, is produced and accumulated excessively as a result of these alterations, which improve amyloidogenic processing of APP [28].

The strongest known genetic risk factor for late-onset Alzheimer's disease (LOAD), which makes up the bulk of cases, is the apolipoprotein E (APOE) ε4 allele. The risk of developing AD is three times higher for carriers of a single ε4 allele and up to fifteen times higher for homozygous carriers than for non-carriers [29]. APOE ε4 worsens neuroinflammatory processes, hinders clearance, and encourages amyloid aggregation [30]. Variants in TREM2, CLU, PICALM, ABCA7, and SORL1, which are linked to endosomal trafficking, lipid metabolism, and immunological control, are additional genetic factors [31].

3.3 Lifestyle and Environmental Aspects

The onset and course of Alzheimer's disease are greatly influenced by environmental and lifestyle factors. Increased tau phosphorylation and amyloid buildup have been connected to head trauma, particularly repetitive mild traumatic brain injuries, which raises the risk of AD [32]. Metabolic disorders such obesity, dyslipidemia, and type 2 diabetes mellitus increase insulin resistance and chronic inflammation, which worsen neurodegenerative alterations [33]. Smoking exacerbates amyloid buildup by causing oxidative stress and cerebrovascular injury [34]. On the other hand, a Mediterranean diet high in antioxidants and omega-3 fatty acids, cognitive function, and physical activity have all been linked to a decreased risk of AD [35]. Additionally, epidemiological research indicates that social interaction and educational attainment may confer cognitive reserve, postponing the emergence of clinical symptoms [36].

3.4 Both Oxidative Stress and Vascular Dysfunction

The importance of cerebrovascular pathology as a contributing factor to Alzheimer's disease is becoming more well acknowledged. Amyloid buildup and tau pathology are accelerated by conditions like hypertension, atherosclerosis, and decreased cerebral blood flow, which decrease the

delivery of oxygen and nutrients to neurons [37]. The blood–brain barrier (BBB) is compromised by vascular dysfunction, which permits immune cells and toxic chemicals to enter and intensify neuroinflammation [38].

Parallel to this, oxidative stress, which results from an imbalance between antioxidant defense and reactive oxygen species (ROS), causes protein oxidation, DNA damage, and lipid peroxidation, all of which contribute to neuronal death [39].

3.5 Mitochondrial dysfunction and inflammation

Alzheimer's disease pathogenesis is characterized by persistent neuroinflammation. Pro inflammatory cytokines such TNF-α, IL-1β, and IL-6 are released by activated microglia and astrocytes and are linked to synaptic dysfunction and neuronal damage [40]. Persistent activation creates a hazardous inflammatory milieu that speeds up the progression of illness, even if inflammation initially acts as a protective mechanism to remove amyloid deposits [41].

Another new etiological factor is mitochondrial dysfunction. Neuronal energy metabolism and calcium homeostasis are disrupted by impaired mitochondrial dynamics, reduced ATP synthesis, and increased ROS formation [42]. These alterations are strongly associated with tau and amyloid pathology, highlighting the pivotal role that failure of energy metabolism plays in Alzheimer's disease [43].

4. PATHOPHYSIOLOGY

Cognitive decline, memory loss, and behavioral abnormalities are the results of Alzheimer's disease (AD), a progressive neurodegenerative illness marked by structural, molecular, and functional changes in the brain [44]. Extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) are two of the neuropathological hallmarks of AD. These buildups set off a series of events that result in synaptic dysfunction, neuronal death, and brain atrophy [45].

4.1 Pathology of Amyloid-β

According to the amyloid cascade hypothesis, an initial step in the pathophysiology of AD is the aberrant buildup of amyloid-β peptides, specifically Aβ42 [46]. Amyloid precursor protein (APP) is sequentially cleaved by β-secretase (BACE1) and γ-secretase to produce Aβ peptides [47]. Soluble Aβ is effectively eliminated under healthy settings, but in AD, either excessive synthesis or poor clearance causes it to aggregate into fibrils, oligomers, and extracellular plaques [48]. High levels of neurotoxicity caused by soluble Aβ oligomers impair memory and learning by interfering with synaptic plasticity, long-term potentiation (LTP), and neuronal signaling [49]. Cognitive decline is associated with the buildup of Aβ plaques, which are mostly seen in the neocortex, hippocampus, and amygdala [50]. Furthermore, Aβ aggregates increase neuroinflammation and neuronal damage by inducing oxidative stress, mitochondrial damage, and microglia activation [51].

4.2 Neurofibrillary Tangles and Tau Pathology

The existence of neurofibrillary tangles (NFTs), which are made of hyperphosphorylated tau protein, is the second main characteristic of AD [52]. Tau normally facilitates axonal transit by stabilizing microtubules inside axons. Tau detaches from microtubules and aggregates form paired helical filaments (PHFs) in AD due to abnormal tau phosphorylation by kinases such GSK-3β and CDK5 [53].

These NFTs build up inside neurons, causing axonal transport problems, cytoskeletal integrity disruption, and ultimately neuronal dysfunction and apoptosis [54]. The clinical stages of cognitive decline correlate to the expected physical course of tau pathology, which begins in the entorhinal cortex and hippocampus and progresses to the neocortex [55]. Additionally, recent research indicates that pathogenic tau behaves like a prion and spreads trans-synaptically [56].

4.3 Neuronal Death and Synaptic Dysfunction

The most powerful pathological correlate of cognitive impairment in Alzheimer's disease is synaptic loss [57]. By changing glutamatergic transmission, decreasing dendritic spine density, and compromising neurotransmitter release, Aβ oligomers and phosphorylated tau both contribute to synaptic dysfunction [58].

Oxidative stress, mitochondrial malfunction, calcium dysregulation, and activation of apoptotic signaling pathways, including caspase-3, all contribute to neuronal apoptosis [59]. Cortical thinning and hippocampus atrophy, which are visible on neuroimaging and correlate with memory loss, are caused by progressive neuronal death [60].

4.4 Degeneration of the Cholinergic System

Degeneration of cholinergic neurons, especially in the basal forebrain (nucleus basalis of Meynert), is a characteristic biochemical marker of AD that leads to a reduction in the synthesis of acetylcholine (Ach) [61]. Acetylcholine is essential for memory, learning, and attention. The cholinergic theory of Alzheimer's disease is based on the direct correlation between cognitive dysfunction and the loss of cholinergic transmission [62]. Acetylcholinesterase inhibitors (AChEIs), such donepezil, rivastigmine, and galantamine, have been developed as a result of this, and they temporarily increase cholinergic signaling and boost cognitive function [63].

4.5 Inflammation of the Neuron

One important secondary mechanism in the pathogenesis of AD is neuroinflammation. In response to tau aggregation and Aβ plaques, activated microglia and astrocytes release reactive oxygen/nitrogen species and pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) that worsen neuronal damage [64]. Chronic activation encourages synaptic pruning, neuronal toxicity, and disruption of the blood-brain barrier, but acute activation might help remove Aβ [65].

Additionally, genetic variations like TREM2 mutations have been linked to altered inflammatory responses, poor Aβ clearance, and an impact on microglial activation [66]. A self-replicating cycle of brain damage is created when tau aggregation, amyloid pathology, and persistent inflammation interact to speed up neurodegeneration [67].

4.6 Network Disruption and Brain Atrophy

The entorhinal cortex, posterior cingulate cortex, and hippocampus regions essential for memory and spatial orientation show gradual loss, according to structural imaging studies [68]. Even in the preclinical phases of the disease, functional imaging (fMRI, PET) shows hypometabolism in the default mode network (DMN) and altered neuronal connections [69]. Alzheimer's disease's worldwide cognitive and behavioral symptoms are caused by this pervasive dissociation between cortical and subcortical areas [70].

5. CLINICAL CHARACTERISTICS

Memory, cognitive function, and functional capacity gradually deteriorate in Alzheimer's

disease (AD), a progressive neurological illness that eventually results in total reliance on caretakers [71]. Each of the three stages of AD's clinical course—early (mild), middle (moderate), and late (severe) is distinguished by unique behavioral and neurocognitive traits [72].

5.1 Mild Early-Stage Symptoms

Episodic memory impairment is the first and most noticeable sign of AD, especially when it comes to acquiring new material or remembering recent events [73]. It is common for patients to miss appointments, misplace items, or ask the same question over and over again [74]. This indicates that the medial temporal lobe and hippocampal regions—which are essential for memory consolidation—were involved early on [75].

Language impairments such anomia, confusion about time or location, and mild executive dysfunction, which makes it difficult to plan or multitask, are other early cognitive alterations [76]. In addition, patients may exhibit mild mood swings including anxiety, impatience, or apathy, which frequently come before overt cognitive problems [77]. At this point, most aspects of daily life are maintained, but complicated instrumental skills like driving, money management, and medicine compliance start to decline [78].

5.2 Symptoms of the Middle Stage (Moderate)

Memory loss deteriorates with AD, reaching remote memory and semantic knowledge [79]. Patients who exhibit topographical disorientation and roaming behavior may get confused about time, place, or familiar faces [80].

The severity of language impairments increases, resulting in decreased vocabulary, circumlocution, and trouble comprehending complicated words [81]. Executive dysfunction results in poor decision-making, trouble addressing problems, and a diminished understanding of one's own state [82].

At this point, agitation, anger, depression, hallucinations, and delusions are common behavioral and psychological symptoms of dementia (BPSD) [83]. Changes in personality, including emotional lability, disinhibition, and social disengagement, are also prevalent [84].

When patients are unable to carry out activities of daily living (ADLs) on their own, such as dressing, bathing, and meal preparation, functional decline becomes apparent [85].

5.3 Severe Late-Stage Symptoms

Significant global cognitive impairment impacting executive function, language, memory, and attention is seen in the late stages of AD [86]. Patients may lose the capacity to speak clearly and become totally reliant on caretakers for personal care [87].

Motor dysfunction, stiffness, irregular gait, and incontinence are the next stages of neurological decline [88]. Patients may experience malnourishment, aspiration pneumonia, infections, and dysphagia (difficulty swallowing) as cortical and subcortical neuronal loss progresses [89].

In the end, those with terminal dementia become bedridden and exhibit extreme rigidity and mutism [90]. Secondary problems such pneumonia, sepsis, or dehydration frequently lead to death [91].

5.4 The Progression and Duration of the Disease

Alzheimer's disease typically lasts 8–12 years from diagnosis to death, though this varies depending on genetic background, comorbidities,

and age of onset [92]. It usually takes several years for moderate cognitive impairment (MCI) to develop into full-blown AD, underscoring the significance of early detection and intervention [93].

6. IDENTIFICATION AND SCREENING

Clinical evaluation, cognitive testing, neuroimaging, and biomarker analysis are all used in the diagnosis of Alzheimer's disease (AD) [94]. In order to optimize care and slow the disease's course, it is best to identify the condition as soon as possible, ideally when moderate cognitive impairment (MCI) from AD is present [95]. For an appropriate diagnosis, the International Working Group (IWG) and National Institute on Aging Alzheimer's Association (NIA-AA) guidelines stress a multimodal approach that integrates biomarker data, imaging, and cognitive tests [96].

6.1 Cognitive Evaluation

The first-line diagnostic method for suspected AD cases is still cognitive testing. The most used instrument for evaluating global cognitive function is the Mini-Mental State Examination (MMSE), which evaluates language, orientation, memory, and visuospatial abilities [97]. Although findings vary by education and culture, cognitive impairment is generally indicated by MMSE scores below 24 (out of 30) [98]. Because it assesses executive processes, attention, and visuospatial abilities all of which are frequently impacted in early AD—the Montreal Cognitive Assessment (MoCA) has a higher sensitivity in identifying mild cognitive impairment [99]. Another standardized tool that is frequently used in clinical trials to track the severity and course of the disease is the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) [100]. In order to distinguish AD from other dementias, neuropsychological batteries may additionally contain the Trail Making Test, Verbal Fluency Test, and Clock Drawing Test [101].

6.2 Methods of Neuroimagin

g Alzheimer's disease diagnosis and staging are greatly aided by structural and functional brain imaging.Cerebral atrophy is detected by magnetic resonance imaging (MRI), particularly in the entorhinal cortex, temporal-parietal areas, and hippocampal regions, which are early sites of neuronal loss in AD [102]. Hippocampal shrinkage can be measured by volumetric MRI, which can be used as a biomarker for the advancement of disease [103].

Despite being less sensitive than MRI, computed tomography (CT) scans can be used to rule out alternative structural causes of dementia, such as vascular lesions, hydrocephalus, or malignancies [104].

Imaging using Positron Emission Tomography (PET) is crucial for both molecular and functional diagnosis. AD-related hypometabolism in the temporoparietal and posterior cingulate cortices is seen by fluorodeoxyglucose PET (FDG-PET) [105]. While Tau PET tracers, such as ^{18}F-flortaucipir, enable mapping of neurofibrillary tangle distribution and are strongly associated with cognitive decline, amyloid PET tracers, such as ^{11}C-PiB, ^{18}F florbetapir, and ^{18}F-flutemetamol, visualize amyloid-β deposition in vivo [106]. Emerging techniques that evaluate white matter integrity and brain connections and offer early illness indicators include diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) [107].

6.3 Alzheimer's Disease Biomarkers

Particularly in the preclinical stage, biochemical biomarkers from blood plasma and cerebrospinal

fluid (CSF) have become essential parts of the diagnosis of AD. Neuropathology is shown in CSF biomarkers: Lower Aβ42 levels are indicative of brain amyloid plaque buildup. Axonal injury and tau pathology are indicated by elevated total tau (t-tau) and phosphorylated tau (p-tau), respectively [108]. A diagnosis of AD is highly supported by a CSF profile with low Aβ42 and high t-tau and p tau [109]. Biomarkers based on blood are becoming more popular as less invasive substitutes. Neurofilament light chain (NfL), p-tau181, and p-tau217 levels in plasma exhibit great diagnostic accuracy and are correlated with the course of the disease [110,111]. In standard clinical settings, they could soon either replace or supplement CSF testing [112]

6.4 Genetic Examination

The main conditions for which genetic testing is advised include familial or early-onset Alzheimer's disease (before age 65). Autosomal dominant types of AD are linked to mutations in the genes for amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2), which raise the synthesis of Aβ42 [113]. The most important genetic risk factor for sporadic AD is the apolipoprotein E (APOE) gene; carriers of the APOE ε4 allele are three to twelve times more likely to develop the illness and do so earlier than non-carriers [114]. However, as APOE testing shows vulnerability rather than certainty of disease, it is not advised for asymptomatic people to do routine testing [115].

7. CURRENT METHODS OF TREATMENT

Alzheimer's disease (AD) is still a significant therapeutic challenge despite a great deal of research, and the medicines that are currently available mostly provide symptomatic alleviation rather than total disease reversal. In order to improve quality of life and postpone functional deterioration, current management options include disease-modifying medications, symptomatic pharmacotherapy, and non-pharmacological measures [116].

7.1 Treatment for Symptoms

7.1.1 Inhibitors of Cholinesterase (ChEIs)

According to the cholinergic theory of AD, acetylcholine (Ach), a neurotransmitter essential for memory and learning, may be deficient in some cases, contributing to cognitive decline. Cholinesterase inhibitors (ChEIs) improve synaptic transmission and cognitive function by stopping the enzymatic breakdown of Ach [117].

Currently, mild to moderate AD is treated with three FDA-approved ChEIs:

For all stages of AD, donepezil is an authorized reversible acetylcholinesterase inhibitor. It enhances behavior, global function, and cognition [118]. According to studies, donepezil delays placement in a nursing home and improves Mini-Mental State Examination (MMSE) results [119].

Rivastigmine: Provides more comprehensive cholinergic support by inhibiting both acetylcholinesterase and butyrylcholinesterase [120]. For patients experiencing gastrointestinal side effects from oral medication, rivastigmine, which comes in oral and transdermal formulations, is especially helpful [121].

Galantamine: Promotes cholinergic neurotransmission by acting as a positive allosteric modulator of nicotinic receptors and an acetylcholinesterase inhibitor [122].

7.1.2 Antagonist for NMDA Receptors

For moderate to severe AD, memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist,

has been authorized [123]. It works by preventing excessive glutamate-induced excitotoxicity, which is a factor in synapse loss and neuronal injury [124]. Particularly when paired with ChEIs, memantine enhances behavior, cognitive function, and functional independence [125].

By focusing on both cholinergic and glutamatergic pathways, combination therapy of donepezil with memantine has been demonstrated to produce synergistic effects in moderate to-severe AD [126].

7.2 Disease-Modifying Therapies (DMTs):

Research in recent years has concentrated on DMTs, which target the underlying pathology, specifically tau aggregation and amyloid-β (Aβ), in order to slow or stop the progression of the disease [127].

7.2.1 Aducanumab

Aduhelm™ is a human monoclonal antibody that selectively binds to aggregated Aβ, promoting plaque clearance through microglial phagocytosis [128]. The FDA granted it accelerated approval in 2021 based on its ability to reduce amyloid burden, although its clinical benefit in cognition is still up for debate [129]. In the EMERGE trial, aducanumab demonstrated a 22% reduction in cognitive decline (measured by CDR-SB) in early AD patients when compared to a placebo [130].

7.2.2 Lecanemab

Targeting soluble Aβ protofibrils, lecanemab (Leqembi™) is a humanized IgG1 monoclonal antibody that lowers plaque development and enhances cognitive function [131]. Following findings from the CLARITY-AD Phase 3 trial, which showed a 27% slowing of cognitive deterioration over 18 months in early AD, it was fully approved by the FDA in July 2023 [132]. Additionally, lecanemab demonstrated improved daily functioning as seen by improvements in ADCS-MCI-ADL (Activities of Daily Living) scores [133].

7.2.3 Donanemab

In 2024, the FDA authorized donanemab, an IgG1 monoclonal antibody that targets the modified and extremely aggregation-prone type of amyloid known as N-terminal pyroglutamate Aβ (Aβp3–42) [134]. Donanemab showed significant gains in cognitive and functional measures in the TRAILBLAZER-ALZ 2 study, which showed a 35% slowing of clinical decline in early symptomatic AD when compared to placebo [135]. ARIA continues to be a dose-limiting adverse effect, similar to other antibodies [136].

7.3 Non-pharmacological and supportive therapies

In addition to medication, non-pharmacological therapies can enhance cognitive and behavioral results and are essential to the comprehensive management of AD [137].

Physical activity: Frequent resistance and aerobic exercise improves the expression of neurotrophic factors (such as BDNF), decreases neuroinflammation, and may postpone cognitive decline [138].

Dietary management: A lower risk of AD progression is linked to the Mediterranean and MIND diets, which are high in antioxidants and omega-3 fatty acids [139].

Psychosocial support: Social interaction, education for caregivers, and counseling lessen caregiver stress and enhance patient wellbeing [140].

8. PREVENTIVE AND LIFESTYLE STRATEGIES

8.1 Exercise

In both observational and interventional research, regular aerobic and resistance exercise is consistently linked to a decreased incidence of Alzheimer's disease (AD) and a slower rate of cognitive decline. Increased cerebral blood flow, brain-derived neurotrophic factor (BDNF), neurogenesis, and synaptic plasticity are all benefits of exercise, especially in the hippocampus, which is a key area for memory. [141,142]

According to meta-analyses, the risk of dementia can be decreased by about 30–40% by participating in moderate-intensity physical activity for at least 150 minutes per week. [143] In patients with mild cognitive impairment (MCI), exercise therapies have also shown benefits in memory performance and executive function. [144]

8.2 Plant-based and Mediterranean diets

There is a substantial correlation between a lower risk of AD and a slower rate of cognitive decline and following the Mediterranean diet (MeDi), which is high in fruits, vegetables, legumes, nuts, olive oil, and fish. [145]

High concentrations of polyphenols, omega-3 fatty acids, and antioxidants found in the MeDi aid in lowering amyloid aggregation, neuroinflammation, and oxidative stress. [146]

A combination of MeDi and DASH, the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) has been demonstrated to reduce AD risk by as much as 53% in groups with strong adherence. [147] According to recent longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), MeDi adherence is associated with retained cortical thickness and decreased amyloid formation. [148]

8.3 Social and cognitive interaction

Even in people with AD pathology, cognitive stimulation from reading, puzzles, bilingualism, and lifelong learning improves cognitive reserve and delays the onset of symptoms. [149] By lowering stress hormones and enhancing synaptic resilience, engaging in social and intellectually stimulating activities (such as volunteering and group hobbies) is associated with a lower risk of dementia. [150]

According to multicenter clinical trials, cognitive stimulation therapy (CST) has demonstrated quantifiable improvements in global cognition and quality of life in high-risk individuals and early AD patients. [151]

8.4 Management of metabolic and vascular risk factors

84 Since AD pathogenesis is influenced by metabolic problems and vascular dysfunction, controlling these risk factors is essential for prevention. The risk of cognitive impairment is considerably reduced by the effective management of obesity, hyperlipidemia, diabetes mellitus, and hypertension. [152]

A multidomain strategy that included cognitive training, exercise, diet, and vascular risk monitoring was shown to enhance or preserve cognitive function over a two-year period by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). [153]

In support of lifestyle-based risk reduction, similar "FINGER-type" multidomain preventive trials are currently being carried out worldwide. [154]

8.5 Stress reduction and sleep hygiene

Recent studies show that prolonged stress and sleep deprivation lead to increased tau phosphorylation and amyloid-β buildup by disrupting glymphatic clearance and raising cortisol levels. [155] Therefore, encouraging enough sleep (7–8 hours per night) and stress-reduction techniques like mindfulness and meditation may help safeguard cognitive function over the long run. [155,156]

9. FUTURE PROSPECTS

9.1 Customized treatment and precision medicine

Precision medicine is the way of the future for managing Alzheimer's disease (AD), using genetic, genomic, and imaging data to customize treatments for each patient. [157,158] To stratify patients by risk, forecast progression, and maximize treatment, this method takes into account APOE genotype, polygenic risk scores, amyloid/tau PET, MRI volumetrics, CSF biomarkers, and plasma profiles. [159]

Clinicians can determine which patients will benefit most from lifestyle changes, disease modifying treatments (DMTs), or combination methods by combining this multidimensional data. [158,160]

9.2 Multi-target drug development

Multi-target therapeutic strategies are being explored in light of the intricate multifactorial pathology of AD, which includes amyloid deposition, tau hyperphosphorylation, neuroinflammation, oxidative stress, and synaptic dysfunction. [161,162] These substances seek to reduce neuroinflammation, stop tau phosphorylation, and inhibit amyloid aggregation all at once. [161]

For instance, early-stage clinical trials are being conducted on hybrid compounds that combine antioxidant activity and cholinesterase inhibition, or amyloid-targeting antibodies with anti-inflammatory adjuncts. [162,163]

9.3 Gene therapy and stem cells for neural regeneration

In preclinical AD models, stem cell therapies employing mesenchymal stem cells (MSCs) or induced pluripotent stem cells (iPSCs) are being researched to replace damaged neurons, repair synaptic networks, and control neuroinflammation. [164,165] Gene therapy techniques, such as CRISPR-based repair of harmful mutations (e.g., PSEN1, APP) or viral vector-mediated delivery of neuroprotective genes (BDNF, NGF), show promise for disease modification in familial and early-onset AD. [166,167]

These methods are promising regenerative treatments that aim to address the underlying cause of neuronal loss rather than just its symptoms, even though practical translation is still in its early stages. [165,167]

9.4 Preventive vaccination and early screening

In order to intervene before clinical symptoms manifest, new research is investigating the preclinical detection of at-risk patients utilizing blood biomarkers, AI-assisted imaging, and polygenic risk grading. [168] In order to generate a safe immune response that could stop or slow the production of plaque and tangles, preventive vaccination techniques that target tau or amyloid-β epitopes are being researched. [169,170] The necessity of population-level screening and risk stratification is highlighted by early immunotherapy trials that indicate vaccination

may be most effective when given before substantial neurodegeneration. [170]

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