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ALZHEIMER'S DISEASE AS A PUBLIC HEALTH AND CLINICAL CHALLENGE: RISK FACTORS, BIOMARKERS, AND TREATMENT STRATEGIES

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Abstract

Introduction and purpose: Alzheimer's disease (AD) is the most common cause of dementia and a growing clinical and public health challenge in ageing populations. Its rising prevalence,

high social and economic burden, and lack of curative therapy highlight the need for better understanding of its mechanisms, risk factors, diagnostic tools, and treatment strategies. This review summarizes current knowledge on AD, with particular emphasis on biomarkers, modifiable risk factors, and emerging therapeutic approaches.

Brief description of the state of knowledge: AD is characterized by extracellular amyloid-β deposition and intracellular accumulation of hyperphosphorylated tau; however, its pathogenesis is multifactorial and also involves neuroinflammation, gliosis, mitochondrial dysfunction, neuronal loss, demyelination, and genetic susceptibility. Age is the strongest risk factor, while low educational attainment, physical inactivity, obesity, cardiovascular risk factors, depression, hearing loss, and social isolation may also increase disease risk. Biomarkers, including amyloid PET, tau PET, cerebrospinal fluid analytes, and blood-based markers such as phosphorylated tau, neurofilament light chain, and glial fibrillary acidic protein, improve early and accurate diagnosis. Current treatment is mainly symptomatic, but anti-amyloid, anti-tau, immunological, and non-pharmacological strategies are under intensive investigation.

Summary: Alzheimer's disease should be viewed as both a neurodegenerative disorder and a public health challenge requiring prevention, early diagnosis, risk reduction, and personalized management. Further advances in biomarkers and targeted therapies may improve diagnostic precision and support more effective care.

Keywords: Alzheimer's disease, biomarkers, amyloid-β, Tau

1. Introduction and purpose

Alzheimer's disease remains an incurable, progressive, and ultimately fatal disease[1]. To better understand this multifactorial disease, it is essential to consider all contributing factors. Focusing solely on amyloid-β and tau aggregation would hinder progress in treatment, diagnosis, and prognosis. Only by accounting for all underlying pathobiological mechanisms such as demyelination, neuronal loss, gliosis, neuroinflammation[2,3], mitochondrial dysfunction[4], microglial response[5], astrocyte dysfunction[6] , and genetic factors[7] can we work toward improving the lives of people with Alzheimer's disease and developing effective treatments to overcome it.

2. Description of the state of knowledge

2.1. Epidemiology

In 2021, 57 million people worldwide were living with dementia, over 60% of whom resided in low- and middle-income countries. Each year, nearly 10 million new cases are reported. Alzheimer's disease accounts for up to 70% of these cases. The global cost of dementia was estimated at approximately USD 1.3 trillion, with around 50% of this burden falling on families or friends, who often provide care for an average of five hours per day.[8] Women are affected by AD dementia nearly twice as often as men[9]. Age remains the most significant risk factor; prevalence increases with advancing age, but also with lower levels of education, the presence of APOE ε4 alleles, and Black or Hispanic ethnicity [10]. The APOE ε4 allele increases the lifetime risk of AD by approximately 20%-30% when one ε4 and one ε3 allele are present, and by up to 40% when two ε4 alleles are present.[11] Most patients have late-onset sporadic Alzheimer's disease (LOAD), while early-onset Alzheimer's disease (EOAD) accounts for 5%-10% of cases. The primary difference between these two variants is the age of symptom onset: in EOAD, symptoms begin before age 65 and may appear as early as in a patient's 30s. Mutations in the APP, PSEN1, and PSEN2 genes are associated with EOAD but are found in only 10%-15% of these cases.[12] While genetic causes are well-characterized in familial AD, the genetic factors contributing to sporadic AD remain poorly understood. Several genes, including ICA1L, DGKQ, ICA1, DOC2A, WDR81, and LIME1, are believed to modulate amyloid precursor protein (APP) metabolism. Other implicated genes, such as RHOH, BLNK, SIGLEC11, LILRB2, and RASGEF1C, are primarily expressed in microglia. Additionally, SHARPIN and RBCK1, which encode components of the linear ubiquitin chain assembly complex (LUBAC) - a regulator of TNF-α signaling and OTULIN, which regulates LUBAC activity, are also of interest.*[13]* According to the Lancet Commission on Dementia Prevention, approximately 40% of dementia cases globally are linked to modifiable risk factors, including lower educational attainment, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption (>21 units/week), air pollution, traumatic brain injury, and social isolation.[14] Recent reviews published in the fields of health sciences and sport sciences support the view that modifiable lifestyle-related factors, particularly physical inactivity, diet, cognitive engagement, and social participation, should be considered important targets in AD prevention strategies.[115-118]

2.2. Clinical signs and symptoms

The initial clinical signs of developing Alzheimer's disease can be subtle and are often overlooked by patients and their families. These symptoms may appear many years before a formal diagnosis of dementia and can range from mood swings, anxiety, and sleep disturbances to depression, impaired judgment, confusion, aggression, and even delusions or hallucinations.[15] Every patient diagnosed with AD experiences mild cognitive impairment (MCI), but not all individuals with MCI have AD-related brain changes. MCI is characterized by measurable cognitive decline with minimal impairment in instrumental activities of daily living (IADLs). While AD can be a cause of MCI, other neurologic, neurodegenerative, systemic, or psychiatric disorders may also contribute to it.[16] Historically, AD diagnosis relied heavily on clinical evaluation, using criteria such as the 2011 National Institute on Aging and Alzheimer's Association (NIA-AA) core clinical criteria for probable Alzheimer's disease dementia. These criteria include: meeting the general definition of dementia, insidious onset, clear history of symptom progression, predominance of one category of symptoms (amnestic or non-amnestic), exclusion of alternative diagnoses.[17] However, due to the limitations of clinical criteria alone, biomarkers, including PET imaging, cerebrospinal fluid (CSF), and blood-based analyses, have become valuable tools in improving diagnostic accuracy. These biomarkers allow for a more precise characterization of AD throughout its clinical continuum. Recent revisions to diagnostic criteria concluded that a single core biomarker is sufficient to establish an AD diagnosis and to inform clinical decision-making. The major core biomarkers and their corresponding detection methods include:

A (Aβ proteinopathy): Detected via Aβ42 in CSF or plasma analytes, or positive amyloid PET imaging

T (phosphorylated and secreted AD tau): detected via phosphorylated tau (p-tau181, p-tau217, p-tau231) in CSF or plasma, or via Tau PET imaging[18]

These biomarkers help define the stages of AD more clearly: Preclinical stage: Individuals are cognitively normal but exhibit AD pathological changes. This stage remains theoretical in some cases, as some individuals may die without ever developing clinical symptoms.[19] The next stage is the prodromal phase, characterized by MCI with subtle deficits - most often in episodic memory - that do not yet meet the criteria for dementia. The final stage is fully developed dementia, marked by widespread cognitive impairments, including difficulties in reasoning, acquiring new information, visual memory, language, and personality changes.

These symptoms interfere significantly with daily life and represent a clear decline from previous levels of functioning.

2.3. Pathophysiology

Amyloid-β peptide is a primary component in the formation of neuritic plaques, a hallmark of Alzheimer's disease. This connection was first identified in 1985, and since then, significant efforts have been made to understand how Aβ contributes to the pathogenesis of AD.[22] The gene encoding the amyloid precursor protein is located on chromosome 21, and Down syndrome, which involves trisomy of this chromosome, is a known risk factor for dementia.[21] Over 90% of individuals with Down syndrome develop dementia, with AD being the leading cause of death and cited on approximately 30% of death certificates in this population.[22–24] APP is a type I transmembrane protein, part of a family that includes APP-like protein 1 (APLP1) and APP-like protein 2 (APLP2). It is involved in several key physiological processes, including neurogenesis, neuronal differentiation, synaptic function, cell adhesion, cell cycle regulation, and calcium homeostasis.[25] APP can be processed through two major pathways: non-amyloidogenic (the primary physiological route) and amyloidogenic. In the non-amyloidogenic pathway, APP is first cleaved by α-secretase, which releases the N-terminal extracellular soluble APP α domain (sAPPα) and a membrane-bound C83 fragment. The sAPPα domain has neuroprotective properties and can inhibit β-secretase activity, thereby preventing the formation of Aβ peptides.[26] Conversely, the amyloidogenic pathway begins with cleavage by β-secretase, producing a soluble APP β fragment (sAPPβ) and a membrane-bound C99 domain. BACE1 (β-site APP-cleaving enzyme 1) is the primary β-secretase and is synthesized in the endoplasmic reticulum (ER) as a proenzyme that undergoes several post-translational modifications in the Golgi apparatus.[27,28] The next step in both pathways involves cleavage by γ-secretase, a multi-subunit transmembrane complex composed of presenilin (PS1 or PS2), presenilin enhancer 2 (PEN-2), nicastrin (NCT), and anterior pharynx-defective 1 (APH-1).[29] Mutations in PSEN1 or PSEN2, the genes encoding presenilins, are known to cause familial forms of AD. In the amyloidogenic pathway, γ-secretase cleaves the C99 fragment, producing various Aβ peptides and the APP intracellular domain (AICD). The Aβ42 isoform, in particular, is prone to aggregation, leading to the formation of plaques and fibrils that are neurotoxic, triggering neuroinflammation, cytotoxicity, and neuronal cell death.[30] In addition to the canonical secretase pathways, APP can also be processed by alternative enzymes. One such route involves cleavage by membrane-bound matrix metalloproteinases, specifically η-secretase (e.g., MT5-MMP), producing soluble APP η (sAPPη) and ηCTF. ηCTF can then be further cleaved by ADAM10

and BACE1, yielding Aη-α and Aη-β peptides; notably, Aη-α has been shown to exhibit neurotoxic properties.[31] There are two additional, less conventional pathways contributing to APP-associated neurotoxicity:

1. Caspase-3 cleavage of APP results in the formation of a C-terminal 31-amino acid peptide (C31), which is cytotoxic.
2. γ-Secretase cleavage produces a fragment known as Jcasp, which also plays a role in neurodegeneration.[32]

Aβ monomers aggregate to form oligomers, which further assemble into fibrils within amyloid plaques. These fibrils stack and contribute to the progressive formation of plaques.[33] Studies have shown that Aβ plaque formation can behave in a prion-like manner. For instance, the injection of brain extracts from AD patients or APP-transgenic mice into other APP-transgenic hosts induces Aβ aggregation in a manner reminiscent of prion seeding. These Aβ aggregates can propagate from neuron to neuron, further mimicking the behavior of prions.[34] There have even been documented cases of iatrogenic transmission of Aβ, where children treated with human cadaveric pituitary-derived growth hormone - contaminated with both prions and Aβ seeds - later developed Aβ pathology.[35] Several molecules have been shown to facilitate Aβ aggregation, including metal ions, glycosaminoglycans, APOE, α-synuclein, and β2-microglobulin (B2M).[36–40] B2M, a component of the major histocompatibility complex class I, has been found within amyloid plaques. Elevated levels of B2M are associated with enhanced Aβ aggregation and increased neurotoxicity in AD brains. Notably, reducing B2M levels using antisense oligonucleotides or monoclonal antibodies has been shown to alleviate neuropathological changes in mouse models of AD.[41]

In 1992, Hardy and Higgins proposed the influential amyloid cascade hypothesis, which posits that the formation of neurofibrillary tangles (NFTs), neuronal loss, and cognitive decline in AD begin with excessive generation and aggregation of Aβ.[42] Supporting this hypothesis is the observation that individuals with Down syndrome, who carry an extra copy of the APP gene, develop increased Aβ deposition and AD-like neuropathology, similar to those with missense mutations in APP. Additionally, the APP-A673T variant, which is associated with a reduced risk of developing AD, lends further support to the amyloid hypothesis. Recent therapeutic advances, particularly monoclonal antibodies targeting Aβ, have shown promise and reinforce the view that Aβ plays a critical role in AD pathogenesis, providing further validation of the amyloid cascade hypothesis.[43,44]

However, not all findings fully support this hypothesis. Some studies have raised doubts about Aβ being the primary driver of dementia.[45] Clinical observations indicate that NFTs correlate more strongly with cognitive decline than Aβ plaques.[46] This has led to a broader view of AD pathophysiology, suggesting that while Aβ aggregation may initiate the disease, other mechanisms-such as tau pathology, neuroinflammation, and synaptic dysfunction-may play equally important roles, or even become dominant as the disease progresses.

2.3.1. Tau

In the normal human brain, tau functions as a microtubule-associated protein that stabilizes microtubule binding.[47] In pathological conditions, however, tau forms NFTs and disrupts normal brain function in other ways, such as impairing APP-mediated iron export in neuronal cells. This impairment leads to toxic iron retention, neuronal loss, and cognitive deficits in mice.[48] Tau aggregation correlates with brain atrophy and cognitive decline more strongly than Aβ deposition.[49] However, NFTs are not exclusive to Alzheimer's disease; they are also found in the brains of elderly individuals without cognitive impairment, or with only mild memory dysfunction, a condition classified as primary age-related tauopathy (PART).[50] Tau is therefore not specific to AD and can be observed in several other conditions, including primary tauopathies such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, frontotemporal dementia (FTD), and PART.[51] The MAPT (microtubule-associated protein tau) gene produces two isoforms based on the number of microtubule-binding domain (MTBD) repeats: 3R tau and 4R tau. In the mature human brain, these isoforms are present in nearly equal proportions. In AD, this balance is maintained, but both isoforms form twisted, insoluble aggregates, resulting in NFTs.[51] Before aggregating, tau undergoes multiple post-translational modifications (PTMs) including phosphorylation, ubiquitination, SUMOylation, acetylation, methylation, glycosylation, and truncation. Hyperphosphorylation is particularly crucial in tauopathy development, as it promotes the formation of pathological, insoluble tau.[52] Ubiquitin is found in NFTs and senile plaques and contributes to tau filament formation and aggregation.[53] SUMOylation-attachment of small ubiquitin-like modifiers (SUMO), also promotes tau phosphorylation, and vice versa. This modification decreases tau solubility and impairs its degradation.[54] Acetylation inhibits tau's normal function, promotes aggregation, and destabilizes the cytoskeleton in the axon initial segment, creating a barrier that tau cannot cross, resulting in its accumulation in axons.[55,56] Methylation, by contrast, appears to be a physiological PTM in the brain and may protect against tau aggregation.[57] Glycosylation also precedes hyperphosphorylation. Specifically, N-glycosylation increases tau's susceptibility to hyperphosphorylation, while O-GlcNAcylation

exerts protective effects. In AD brains, O-GlcNAc-modified tau is deficient, and blocking this modification further increases tau phosphorylation.[58,59] Truncated tau results from cleavage by enzymes such as caspases and asparagine endopeptidase (AEP). For example, caspase-2 cleaves tau at D314 to form Δtau-314, and caspase-3 produces Δtau-421. These truncated forms are more prevalent in AD brains. Δtau-314 has been shown to initiate neurodegeneration in mice, though it does not cause synaptic dysfunction on its own. Reducing caspase-2 levels restored memory function in animal models.[60,61] AEP becomes more active with age, cleaving tau and impairing its microtubule-stabilizing function, leading to aggregation and neurodegeneration. Inhibiting AEP reduces tau hyperphosphorylation, improves cognition, and prevents neurodegeneration in mice.[62] NFT formation typically begins in the transentorhinal and entorhinal cortex, and progresses to the fusiform and lingual gyri of the neocortex. Disease severity increases with this propagation.[63] Tau appears to spread in a cell-to-cell manner, resembling transmissible pathogens. However, unlike prions, there is no evidence that tau aggregates are infectious. Endolysosomal dysfunction plays a key role in tau fibril expansion. Disruption of lysosomes increases endogenous tau aggregation in neurons.[64] Deletion of phosphatidylinositol-4 kinase type 2α (PI4K2A)-crucial for phosphoinositide-initiated membrane tethering and lipid transport (PITT)-leads to lysosomal storage disease and promotes tau fibril spread.67 Tau pathology and Aβ plaque formation are deeply interconnected in AD. In transgenic mouse models, injection of tau into mice with pre-existing Aβ plaques resulted in tau aggregation in dystrophic neurites surrounding plaques, as well as in NFTs and neuropil threads, highlighting the synergistic pathology.[66]

2.3.2. Neuronal loss

In the healthy ageing brain, neuronal loss is relatively limited. In AD, however, there is a high degree of neuronal cell death in many areas critical for memory and cognitive function. Protective mechanisms that normally limit entry into cell death pathways become dysfunctional. Several regulated cell death mechanisms are involved, including necroptosis, pyroptosis, apoptosis, ferroptosis, and autophagy-dependent cell death.[67] Necroptosis plays a crucial role in neuronal death in AD brains, where upregulation of the long noncoding RNA MEG3 induces necroptosis. Downregulation of MEG3 and inhibition of necroptosis in mouse models with xenografted human neurons prevent neuronal cell loss.[68] Similarly, in APPswe/PS1dE9 transgenic mice, cerebral NLRP1 levels are upregulated, and amyloid-β increases NLRP1-mediated caspase-1-dependent pyroptosis. Knocking down NLRP1 or caspase-1 reduces pyroptosis and cognitive impairment.[69] Ferroptosis depends on intracellular iron, which explains why elevated iron levels are linked to AD. Blocking ferroptosis decreases

neuronal cell death and memory impairment.[70] The accumulation of amyloid-β and tau in neurons has also been shown to induce apoptosis and impair autophagy in AD brains. Moreover, neuronal senescence is associated with dysfunctional autophagy.[71] In addition to these mechanisms, Death Induced by Survival gene Elimination (DISE) is activated by short RNAs. DISE targets hundreds of C-rich 6-mer seed matches in genes essential for cell survival, thereby triggering neuronal death pathways via the RNA-induced silencing complex (RISC). In AD mouse models, RISC preferentially selects more toxic 6-mer seeds. Inhibiting RISC reduces DNA damage and neuronal loss.[72] Together, these mechanisms demonstrate that multiple therapeutic strategies may be pursued for Alzheimer's disease. Further research is essential to identify the precise triggers and pathways of neuronal cell death.

2.3.3. Demyelination

Cortical myelin damage has been detected by macroscopic brain imaging in patients with AD during the preclinical phase, suggesting that demyelination may be an early indicator of brain pathology.[73] In AD mouse models, oligodendrocytes show distinct transcriptomic changes. Both in these models and in AD patients, a specific population of oligodendrocytes - disease-associated oligodendrocytes (DAOs) - can be identified, and they play a crucial role in disease pathology. Furthermore, analyses of RNA from AD brains reveal changes in myelin-related genes, indicating that demyelination contributes to AD progression.[74,75] The importance of myelination is also highlighted by the fact that patients with multiple sclerosis are at higher risk of developing AD or dementia. Myelin dysfunction and demyelinating injuries increase amyloid-β plaque accumulation in both AD mouse models and models of experimental autoimmune encephalomyelitis.[76,77] These findings emphasize the role of myelin and oligodendrocyte function in healthy brains, suggesting another potential therapeutic target for treating or slowing the progression of AD.

2.3.4. Gliosis and neuroinflammation

Astrogliosis and microgliosis are prominent features of AD pathophysiology and play an important role in disease progression. The strongest genetic risk factor for AD, APOEε4, is predominantly expressed in astrocytes and microglia.[78] Additional genetic factors, including single nucleotide polymorphisms and rare coding variants in immune-related genes such as TREM2, BIN1, CLU, CR1, PICALM, CD33, and the MS4A gene cluster, have also been identified through WGS and GWAS as AD risk factors.[79] The blood–brain barrier (BBB) is essential for maintaining central nervous system homeostasis. Its disruption - caused by amyloid-β, tau, or systemic inflammation linked to chronic conditions such as obesity,

diabetes, cardiovascular and cerebrovascular disease, or microbial infections - allows immune cells, cytokines, and microbes to enter brain tissue. This initiates inflammatory responses, leading to microglial and astrocytic activation, amyloid plaque formation, tau pathology, and ultimately neuronal degeneration.

2.3.4.1. Microglia

Microglial activation correlates strongly with tau aggregation and amyloid plaque deposition in patients with both MCI and AD.[80] Microglia, the brain's resident immune cells, exhibit diverse phenotypes: lipid droplet–accumulating microglia (common in APOEε4/ε4 carriers), terminally inflammatory microglia (TIMs), and dystrophic (senescent) microglia. Each of these subtypes is associated with impaired amyloid-β clearance and tau pathology, underscoring the multiple roles of microglia in AD.[81–83] Transcriptomic and epigenetic studies show that noncoding AD risk loci promote lipid processing and inflammatory microglial states, linking them to AD progression and severity.[84] Microglia express numerous amyloid-β receptors, including TREM2, LRP1, TLRs, CR3, CD14, CD47, CD36, α6β1 integrin, and RAGE, which mediate processes such as phagocytosis, inflammation, and amyloid clearance. For example, complement C3 and its receptor CR3 contribute to microglial clearance of amyloid-β.[85,86] A study demonstrated that expression of C3 and its receptor C3aR1 positively correlates with cognitive decline and Braak staging in human AD brains. Deletion of C3ar1 in PS19 mice reduced tau pathology, neuroinflammation, synaptic deficits, and neurodegeneration.[87] Microglia also facilitate tau spreading and neurotoxicity by phagocytosing tau-containing neurons or synapses and secreting tau in exosomes, transmitting it to other neurons. Depleting microglia with the CSF1R inhibitor PLX3397 decreased the progression of tau pathology in mice.[88]

2.3.4.2. Astrocytes

Astrocytes, the most abundant glial cells in the CNS, regulate extracellular fluid and neurotransmitter balance, promote synapse formation, and provide metabolic and neurotrophic support. They also contribute to the glymphatic system, in which aquaporin-4 aids in clearing tau and amyloid-β from brain tissue. In APP/PS1 mice, aquaporin-4 deficiency led to increased amyloid deposition, cerebral amyloid angiopathy, synaptic protein damage, and cognitive dysfunction.[89] Reactive astrocytes may play a protective role in slowing AD progression. In mice lacking glial fibrillary acidic protein and vimentin, there was increased amyloid aggregation and neuronal damage.[90] Likewise, Nrf2 activation in astrocytes reduced amyloid deposition and tau phosphorylation, improving cognitive function.[91] This

highlights the importance of astrocytes in reducing amyloid plaque spread and tau pathology. However, astrocytes can also contribute to tau propagation. iPSC-derived astrocyte cultures process tau-laden dead neurons but fail to degrade them, promoting tau spread.[92] In AD, FTD, and rTg4510 tau-transgenic mice, elevated levels of TFEB - a regulator of lysosome biogenesis - have been detected. TFEB amplifies lysosomal function and enhances tau uptake, while overexpression of TFEB suppresses tau propagation and disease progression.[93] Conversely, disruption of TFEB–v-ATPase interactions causes lysosomal dysfunction and worsens tau pathology in mouse models, showing that astrocytes play a crucial role in modulating tau pathology.[94] Tau oligomers can also trigger astrocytes to release high mobility group box 1 (HMGB1), a nuclear protein that induces astrocytic senescence. Inhibiting HMGB1 prevents astrocyte senescence, reduces neuroinflammation, and improves cognitive function in both mice and astrocyte cell culture models.[95]

2.4. Biomarkers

Currently, the only way to confirm Alzheimer's disease with absolute certainty is through histological examination of brain tissue after death. This is why continuous research into biomarkers is crucial for developing more effective diagnostic criteria for AD at its earliest stages.

2.4.1. Imaging biomarkers

MRI remains a fundamental tool in diagnosing and monitoring neurodegenerative diseases, providing detailed information about brain atrophy and helping to rule out alternative causes.[96] Another valuable method is ^18F-FDG PET, which can serve as a marker of AD progression by revealing brain hypometabolism, a process linked to the severity of cognitive decline.[97] Additional imaging techniques include Aβ PET, which enables detection of early amyloid-β aggregation, and tau PET, which highlights tau deposition in brain regions critical for cognition. Interestingly, tau PET findings often overlap with hypometabolic regions seen on ^18F-FDG PET.[98] Despite their usefulness, PET scans are costly and require highly specialized facilities, which limits their accessibility. This has driven interest toward fluid biomarkers as more practical alternatives, offering high sensitivity with fewer logistical challenges.

2.4.2. Fluid biomarkers

Among amyloid-β species, Aβ40 and Aβ42 differ in their propensity to aggregate. Aβ42 is more prone to forming insoluble plaques, leading to reduced CSF and plasma levels of Aβ42

and a decreased Aβ42/Aβ40 ratio, changes that correlate with PET findings.[99] Tau protein is another widely used biomarker, detectable in both CSF and plasma, though plasma tau has lower sensitivity. A newer candidate, brain-derived tau (BD-tau), shows greater accuracy in distinguishing AD from other neurodegenerative conditions.[100] Specific phosphorylated tau isoforms in CSF (T181, T217, and T231) help differentiate Aβ PET-negative from Aβ PET-positive patients in the early stages of AD.[101] p-tau217 stands out as the most promising plasma marker, sometimes even outperforming CSF-based diagnostics.[102] Neurofilament light chain (NfL), reflecting neuroaxonal degeneration, correlates with brain atrophy, hypometabolism, and cognitive decline and can be measured in both CSF and blood.[103] Glial fibrillary acidic protein (GFAP), a marker of astroglial activation, has also emerged as a predictor of AD pathology and of conversion from MCI to AD dementia.[104] CSF sampling remains cost-effective, scalable, and allows assessment of multiple biomarkers simultaneously, but its invasiveness (via lumbar puncture) and lack of spatial resolution are drawbacks. Blood-based biomarkers are more accessible, yet similarly fail to localize pathology. The biggest challenge in biomarker development remains improving diagnostic precision. Achieving this will not only enable earlier and more reliable diagnosis but also help optimize therapeutic strategies.

2.5. Treatment

At present, no curative therapy for Alzheimer's disease exists. Current pharmacological options include three cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine. These provide only symptomatic relief, temporarily maintaining cognitive function but not altering disease progression.[105] Immunotherapies have recently gained traction, particularly monoclonal antibodies targeting amyloid-β. Lecanemab, a humanized IgG1 antibody against soluble Aβ protofibrils, delayed cognitive decline by approximately five months over an 18-month period compared to placebo.[106] While encouraging, these effects are modest, and safety concerns, including amyloid-related imaging abnormalities (ARIA), highlight the need for further refinement. Parallel efforts target tau pathology, which correlates more closely with symptom severity than Aβ. Tau-directed therapies include vaccines (AADvac1, ACI-35) and monoclonal antibodies (e.g., APNmAb005, E2814, JNJ-63733657, Lu AF87908, MK-2214, PNT001, PRX005, semorinemab, and bepranemab).[107] For instance, E2814, a humanized IgG1 antibody targeting the HVPGG epitope within tau's microtubule-binding domain, reduced tau seeding, spreading, and deposition in mouse models.[108] Another approach, MAPTRx, an antisense oligonucleotide, successfully lowered CSF tau levels and was well-tolerated in a phase 1b trial in mild AD

patients.[109] Another therapeutic approach is the TREM2 agonist antibody AL002; repeated administration has been shown to reduce amyloid deposition and increase plaque-associated microglia in mice.[110] Moreover, masitinib, a tyrosine kinase inhibitor targeting mast cells and microglia, has shown potential in alleviating symptoms in patients with mild to moderate AD.[111] Another potential treatment strategy is 40 Hz gamma-sensory stimulation, which reduced phosphorylated tau, amyloid plaques, and inflammatory responses in microglia, thereby helping to maintain cognitive function in AD mice.[112] However, another mouse study questioned these results, reporting that 40 Hz stimulation had no effect on amyloid plaque aggregation or microglial response.[113] A recent six-month trial of visual and auditory 40 Hz gamma-sensory stimulation showed less white matter atrophy and myelin loss in treated patients than in those receiving placebo.[114] Many researchers are pursuing the goal of developing a cure, or at least disease-modifying therapy, using more personalized immunological treatments and other promising strategies. In addition to pharmacological and immunological strategies, structured physical exercise may serve as an important complementary, non-pharmacological intervention aimed at supporting cognitive function, neuroplasticity, quality of life, and functional independence in patients at risk of or affected by AD.[116-118]

3. Conclusions

Alzheimer's disease remains a complex, multifactorial, and progressive neurodegenerative disorder that poses a major clinical and public health challenge. Although amyloid-β and tau pathology remain central to current models of disease development, growing evidence shows that neuroinflammation, gliosis, demyelination, neuronal loss, genetic susceptibility, ageing, and modifiable lifestyle-related factors also play important roles in disease onset and progression. Early detection is crucial for improving patient care and for implementing emerging disease-modifying therapies at the most appropriate stage. For this reason, the development of sensitive, specific, and accessible biomarkers, particularly blood-based biomarkers, remains one of the most important directions in current AD research. At the same time, future management strategies should combine advances in biomarker-guided diagnosis with more personalized therapeutic approaches targeting multiple pathological pathways. In conclusion, further progress in prevention, early diagnosis, and treatment may improve outcomes for patients with Alzheimer's disease and reduce the growing burden of this condition on individuals, caregivers, and healthcare systems. Therefore, preventive strategies should also address modifiable lifestyle factors, including regular physical activity, dietary

habits, cognitive engagement, and social participation, as complementary elements of population-level AD risk reduction.[115-118]

Disclosure

Supplementary Materials

Not applicable.

Author Contributions

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Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve grammar, language clarity, and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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