UPDATE ARTICLE

Unlocking the Future of Alzheimer's Disease: Innovations in Diagnosis and Therapy

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Abstract

Alzheimer's disease (AD) is one of the most common forms of dementia, making up around two thirds of all dementia cases globally. Despite its high prevalence, it is estimated to remain undiagnosed in 41 million people with dementia, and with only about 25% of dementia individuals being clinically identified. AD is the major neurodegenerative disorder leading to dementia, characterized by neuronal atrophy and loss. The accumulation of toxic amyloid-beta (Aβ) oligomers, protein aggregates, along with the formation of neurofibrillary tangles (NFTs) within neurons, is the key pathological feature of AD. NFTs are composed of hyperphosphorylated tau protein. These abnormalities contribute to a decline in cerebral glucose metabolism in the brain, synaptic dysfunction, and mitochondrial impairment. The progression of AD occurs in three stages: (1) the presymptomatic stage, (2) mild cognitive impairment (MCI), and (3) the clinical stage of AD. Many biomarkers have been identified for diagnosing AD and differentiating it from atypical AD. It has emerged as a key area of research, offering significant potential for early detection of AD, prognostication, as well as planning drug therapy and monitoring.

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Introduction

Auguste Deter, a woman from Germany who was admitted to a psychiatric institution in 1901 at the age of 51, was the first patient diagnosed with Alzheimer's disease (AD). She had exhibited signs of severe memory loss, confusion, and disorientation, which were initially misunderstood as a form of senile dementia, but the attending physician, Dr Alois Alzheimer, noticed unusual patterns in her cognitive decline. Dr Alzheimer carefully documented her case by noting her memory problems, hallucinations, and changes in her behavior. After her death in 1906, Dr Alzheimer performed an autopsy on her brain, revealing two key features that would become hallmark characteristics of the disease: neurofibrillary tangles (NFTs) made up of tau protein and amyloid plaques. These specific pathological features led Dr Alzheimer to recognize the disease as distinct from other forms of dementia. Eventually, this condition was named "Alzheimer's disease (AD)" in honor of Dr Alzheimer's pioneering work, and his observations of Auguste Deter's case laid the foundation for the study and understanding of this progressive neurodegenerative disorder.

Alzheimer's disease is a neurodegenerative disorder having diverse pathological subtypes and clinical manifestations. It is defined by distinctive neuropathological changes, including the presence of amyloid plaques, containing aggregated amyloid-beta (Aβ), and NFTs formed of tau aggregates. Over time, these plaques and NFTs lead to neuronal atrophy, synaptic loss, deficiencies of neurotransmitters, neuroinflammation, as well as reactive astrogliosis, eventually, all of these result in cognitive decline. In total, 50–70% cases of neurodegenerative dementias are constituted by AD. Around 44 million people globally are currently living with dementia, and this figure is expected to triple by 2050 as the global population continues to age.[1] In 2020, healthcare costs associated with dementia care were estimated at $305 billion.[2] It accounts for the huge economic burden in the United States, surpassing that of cancer as well as cardiovascular disease. Efforts to develop effective treatments for AD are ongoing, but with mixed results. It is believed that once a certain neuropathological threshold is reached, therapeutic interventions may no longer be effective in altering the disease's course.

Pathophysiology

Alzheimer's disease is a progressive condition that damages the brain, causing a gradual decline in memory and cognitive function. It is marked by the buildup of abnormal protein clumps in the brain, which disrupt normal brain activity and lead to the symptoms of the disease. These plaques develop when amyloid precursor protein (APP) is cleaved incorrectly, causing Aβ peptides to clump together and accumulate between neurons, interfering with synaptic function. Tau, a protein involved in stabilizing microtubules, becomes hyperphosphorylated in AD, which leads to the formation of NFTs inside the neurons. Abnormalities in cellular functions, such as protein misfolding or accumulation, can indeed trigger a chain reaction that involves inflammation, oxidative stress, and neuronal damage. This cascade can disrupt communication between neurons and ultimately lead to cell death. With further progression of disease, there is a significant loss of brain volume in the areas vital for higher cognitive functions, particularly in the hippocampus and cortex. Pathophysiology of AD is further complicated by genetic, environmental, and lifestyle factors, and while the exact cause remains unclear, the accumulation of these pathological changes is central to the progression of the disease. The changes in cerebrospinal fluid (CSF) Aβ levels have been detected quite early, as early as 25 years before it could manifest clinically in patients with hereditary AD. The changes in CSF phosphorylated tau (P-tau) may occur approximately 10 years before the symptom onset.[3] The gradual buildup of tau and Aβ pathologies, leading to cellular dysfunction in the brain, causes neurodegeneration that typically occurs just before the clinical onset of AD, such as cognitive decline.[4]

As per various epidemiological studies, inflammation is shown to be linked between AD and factors such as previous infections or diabetes, in initiating AD pathology.[5] Aβ can trigger an activation response in these immune cells, leading to the release of chemokines and local inflammation.[5,6]

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This inflammation impairs Aβ clearance and promotes tau phosphorylation, leading to ensuing neurodegeneration[7] (Table 1). The sustained inflammatory response not only contributes to neuronal damage but also impairs synaptic function and plasticity, key processes involved in learning and memory. The National Institute on Aging–Alzheimer's Association (NIA-AA) developed a new research framework for diagnosing AD. Using an A/T/N classification system, for AD biomarkers, this framework shifts the focus from a symptomatic to a biological perspective. In A/T/N system, "A" refers to the concentration of Aβ biomarkers, "T" represents tau biomarkers, and "N" indicates neurodegeneration biomarkers. Based on their pathological mechanisms and their role in the disease's progression, this classification helps in the categorization of AD markers.[8] Diagnostic utility of A/T/N system for AD could be further enhanced by incorporating additional markers as Lewy body pathology, brain vascular changes, as well as neuroinflammation.[9]

In AD, the brain experiences a persistent, low-level inflammatory response primarily driven by microglia, the immune cells of the central nervous system. In a healthy brain, microglia help maintain balance and clear cellular debris. However, in AD, they become overly activated by the presence of Aβ plaques and tau tangles. This activation triggers the release of proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6, which intensify neuroinflammation.

Biomarkers of Alzheimer's Disease

The identification of biomarkers for AD has become a crucial area of investigation. It is due to its potential for early detection, prognosis, and treatment monitoring. Various approaches are being investigated to monitor AD progression, including the use of plasma-based markers such as tau protein, Aβ, and neurofilament light polypeptide (NFL). Monitoring these markers holds great potential for the early diagnosis of AD and for assessing the effectiveness of Aβ-targeting therapies, ultimately improving clinical decision-making and patient outcomes. Along with other pathological proteins, recent literature highlights the significant potential of Aβ and tau, as the biomarkers for diagnosing AD and assessing disease progression. Beyond these proteins, additional promising biomarker categories have emerged, including those associated with neurodegeneration, inflammation, and lipid metabolism, which are increasingly being explored to further understand the multifaceted nature of AD.

A major obstacle in advancing AD biomarkers is the invasive nature of existing diagnostic methods. Methods such as positron emission tomography (PET) imaging and CSF protein testing provide valuable insights but are both invasive and expensive. Consequently, there is a concerted effort to identify less invasive, yet reliable, biomarkers derived from fluids such as ocular, blood, saliva, and olfactory fluids.[11] These noninvasive biomarkers have the potential to overcome the limitations of current diagnostic methods, offering a more accessible means for the timely diagnosis and monitoring of course and treatment of AD (Table 2).

The latest clinical guidelines from the International Working Group have updated the diagnostic criteria for AD, highlighting the significance of distinct AD phenotypes and supporting biomarker evidence. These guidelines propose that the cognitively

Table 1: Critical role of inflammatory markers in the pathophysiology of AD and contribution to its progression[10]

Inflammatory marker	*Role*	*Associated effect*
Microglia	Brain's immune cells, central in neuroinflammation in AD	Respond to amyloid plaques, modulate immune response
ABCA7	ATP-binding cassette transporter involved in lipid transport	Mutations increase AD risk, affects microglial function
CD33	A receptor that affects immune responses and microglial activation	Alters microglial activity, linked to AD susceptibility
CR1	Complement receptor involved in immune responses	Involved in clearing amyloid plaques and neuroinflammation
EPHA1	Gene regulating neuronal growth and synapse function	May influence synaptic function and neuroinflammation
MS4A	Family of proteins involved in immune responses	Variations linked to AD, affecting microglial activation
TREM2	Expression of triggering receptor on myeloid cells, involved in microglial activation	Affects microglial response to neurodegeneration
IL-1α, IL-1β	Proinflammatory cytokines that activate inflammatory pathways	Raise neuroinflammation, contribute to cognitive decline
IL-6	Proinflammatory cytokines are elevated in AD	Drives neuroinflammation and exacerbates cognitive decline
CCL2 (MCP-1)	Monocyte chemoattractant protein, a chemokine that attracts immune cells	Increased levels in AD, recruit immune cells to the brain
IL-8	Proinflammatory cytokine involved in immune cell recruitment and BBB permeability	Elevated in AD, linked to inflammation and BBB dysfunction
SDF-1	Stromal cell-derived factor 1, a chemokine that helps attract immune cells	Contributes to immune cell recruitment in neuroinflammation
Progranulin	A growth factor that supports neuronal survival and regulates microglia	Elevated before clinical symptoms, modulates neuroinflammation
YKL-40	Chitinase-3-like protein 1 is involved in the inflammation response	Increased in AD, correlates with cognitive decline
ICAM-1	Intercellular adhesion molecule-1 (ICAM-1) plays a key role in promoting immune cell adhesion to the blood–brain barrier (BBB)	Elevated in AD, linked to microvascular changes and inflammation
VCAM-1	Like ICAM-1, vascular cell adhesion molecule-1 is also involved in immune cell adhesion	Elevated in AD, promotes immune cell infiltration into the brain
IL-33	Cytokine involved in inflammation has a protective role in AD	Downregulated in the brain, but elevated in plasma; affects cognition
sST2 (soluble ST2)	Soluble receptor for IL-33 modulates IL-33's protective effects	Elevated in AD, possibly contributes to cognitive decline

Table 2: Various methods and biomarkers, key blood-based and fluid biomarkers, and the use of ocular markers, particularly retinal degeneration *via* advanced imaging technologies such as OCT in early Alzheimer's disease diagnosis other neurodegenerative diseases, along with their strengths and limitations[11,12]

Diagnostic marker	*Method*	*Description*	*Notes*
Brain atrophy	Structural MRI	Detects brain shrinkage (atrophy) associated with Alzheimer's disease (AD)	–
Brain metabolism	18F-2-fluoro-2-deoxy-D-glucose [FDG (18F)] PET	Measures brain metabolism to detect early AD changes	–
Amyloid deposits (Aβ plaques)	Amyloid-PET	Helps in the quantification of amyloid deposits in the brain	–
Tau protein deposits	Tau-PET [flortaucipir (18F)]	Quantification of tau deposits, especially pathologic tau	Can precede clinical symptoms by several years, important for pre-AD detection
CSF Aβ1-42	CSF sampling	Measurement of amyloid-β protein in cerebrospinal fluid (CSF)	High diagnostic accuracy, especially in combination with other biomarkers
Hyperphosphorylated tau (P-tau)	CSF sampling	Measurement of hyperphosphorylated tau peptide in CSF	High diagnostic accuracy when combined with other biomarkers
Total tau (T-tau)	CSF sampling	Measurement of total tau protein in CSF	High diagnostic accuracy, especially in combination with other biomarkers
Mixed pathologies	Various (CSF, PET, MRI)	Detection of mixed pathologies (AD with other neurodegenerative diseases)	Detection remains difficult and could lead to misdiagnosis
Blood-based and fluid biomarkers	*Type*	*Description*	*Notes*
Biomarker			
Tau (plasma)	Blood-based	Measures tau protein in plasma for AD detection	Emerging biomarker, compatible with primary healthcare settings
miRNAs (various)	Blood-based (plasma, serum, CSF)	Small RNA molecules that regulate gene expression related to cardiovascular diseases, cancer, and neurodegenerative disorders	miRNA expressed in the CNS and influencing brain physiology, aging, and mental illness
miRNAs (in AD)	Blood-based (plasma, serum, CSF)	Specific miRNAs targeting key disease genes related to Alzheimer's disease	May have neurodegenerative or neuroprotective effects in AD
Ocular marker	*Method*	*Purpose/description*	*Notes*
Retinal degeneration	Optical coherence tomography (OCT)	Detects changes of retina linked to AD	Studies in animal models and human patients have shown retinal changes associated with AD
Retinal changes (presymptomatic)	OCT	Retinal changes detection in patients before clinical symptoms of dementia appear	Correlates retinal changes in AD patients in asymptomatic stage

unimpaired, biomarker-positive individuals should be considered potential candidates to progress to the symptomatic stage. As biomarkers become more widely available, they will aid in distinguishing between various neurodegenerative disorders and targeting individuals at increased risk for the clinically symptomatic stage.

Despite these complexities, both typical and atypical phenotypes of AD generally present the canonical biomarkers, including molecular neuroimaging and fluid biomarkers. These tools enable *in vivo* confirmation of AD pathology and enhance diagnostic accuracy, contributing to the growing understanding of AD's clinical and biological heterogeneity.

Genetics of Alzheimer's Disease

Genetics has a major role to play in the predisposition to AD. Although the majority of AD cases are sporadic, familial AD, which represents <5% of cases, is directly associated with genetic mutations. The apolipoprotein E ε4 genotype (APOE-e4) allele, the most recognized genetic factor, is associated with a substantially higher risk of developing late-onset AD. People who carry one copy of the APOE-e4 allele face an increased risk, and those with two copies have an even greater risk, although it does not guarantee the development of the disease. Other genetic variants, such as mutations in the genes APP, presenilin 1 and 2 (PSEN1 and PSEN2), are linked to autosomal dominant forms of early-onset AD.[13] However, it is pertinent to understand that genetics alone does not determine the onset of AD; lifestyle and environmental factors play a crucial role.

Clinical Manifestations

Table 3 summarizes the diverse presentations of AD, emphasizing that the challenge of diagnosing this entity may be related to its heterogeneous nature and the influence of coexisting pathologies.

Diagnosis

A comprehensive evaluation of a patient with memory loss is mandatory to diagnose AD including a thorough history, detailed cognitive assessment, along with other relevant investigations. Details of symptoms such as recent memory impairment, confusional episodes, and difficulty performing daily tasks need to be inquired about. Cognitive examination in the form of Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and detailed lobe batteries helps in the assessment of person's memory, problem-solving abilities, and executive functions. Imaging techniques, such as CT scan head, magnetic resonance imaging (MRI) or PET scan can help exclude other potential causes and detect specific brain changes, including atrophy or amyloid plaques (Fig. 1). Blood tests are increasingly being used to rule out other conditions or detect specific biomarkers, such as amyloid and tau proteins, that may indicate AD. Additionally, genetic testing can be considered in certain cases, particularly when early-onset AD is suspected. While no single test can definitively diagnose AD, imaging can help establish a diagnosis and rule out other causes of cognitive impairment.

Role of Imaging

Imaging plays an important role in differentiating the asymptomatic stage of AD, mild cognitive impairment (MCI), and symptomatic AD by providing objective insights into brain changes and helping differentiate Alzheimer's from other cognitive disorders.[16,17]

Asymptomatic or Preclinical Alzheimer's Disease

In the early phase, patients show no significant symptoms of cognitive decline, but subtle changes in the brain may already be present. Advanced imaging techniques, such as PET, help detect Aβ plaques and tau aggregates, which are hallmarks of AD. In the absence of cognitive symptoms, amyloid deposits in certain areas of the brain may signal an increased risk of developing AD in the future. Functional MRI (fMRI) may also show changes in brain activity and connectivity patterns that can be early signs of AD before clinical symptoms appear.

Mild Cognitive Impairment

Mild cognitive impairment is marked by a noticeable decline in cognitive abilities that exceeds what is typical for a person's age, though it is not severe enough to be classified as dementia. In this stage, imaging can reveal early signs of neurodegeneration. MRI scans may show hippocampal atrophy, a common feature of AD-related MCI, which is associated with memory problems. PET scans can also detect amyloid and tau deposits, helping to predict which MCI patients may progress to AD (Fig. 2B). Fluorodeoxyglucose (18F) (FDG)-PET imaging can highlight areas of decreased glucose metabolism, often seen in the parietal and posterior cingulate regions, which are sites of early neuronal dysfunction in AD.

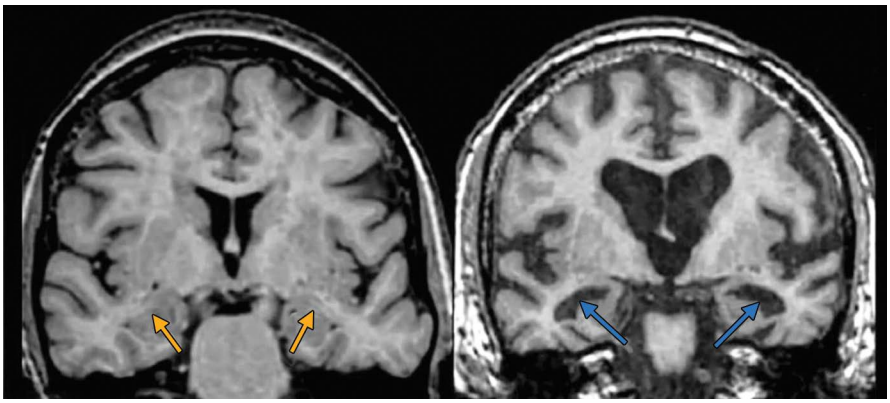
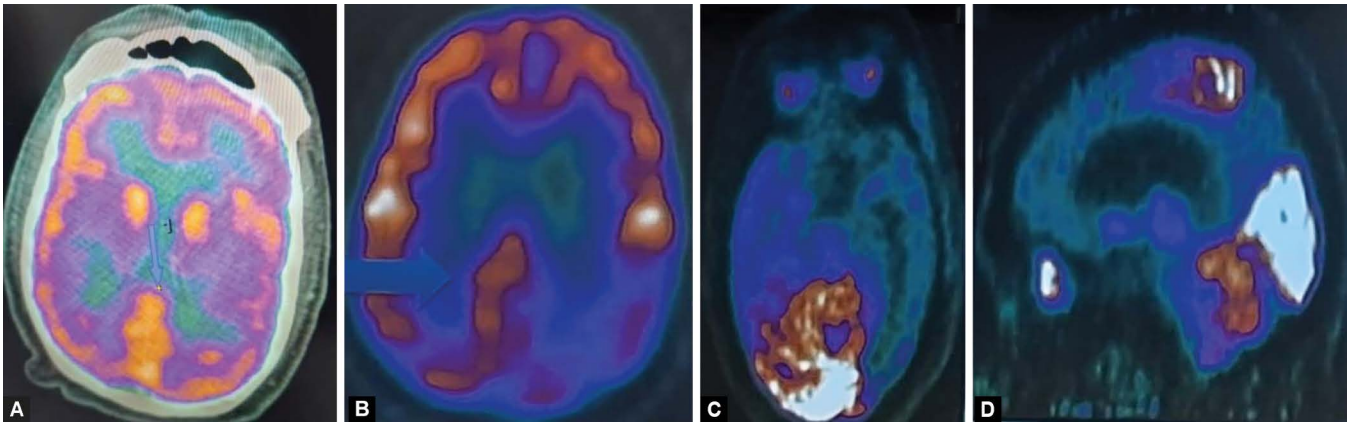


Fig. 1: MRI brain, coronal section (left side) shows normal volume of hippocampus bilaterally (orange arrows) of normal brain, on the right side shows atrophy of bilateral hippocampus (blue arrows) of a patient with AD

Table 3: The clinical manifestations of AD, highlighting its various presentations and subtypes[14,15]

Clinical manifestation	*Description*
Amnestic syndrome (most common, ~85%)	Recognized by significant deficits in learning and short-term memory. Patients have difficulty in recalling newly acquired information. Assessments done by using MMSE, MoCA, Wechsler Memory Scale (WMS), semantic cueing techniques, showing poor recall, and difficulties with information retrieval
Logopenic variant primary progressive aphasia (lvPPA)	Involves problems in motor speech abilities (phonemic paraphasia), single-word retrieval, and sentence repetition may be difficult. Linked to damage in the left perisylvian language areas of the brain
Posterior cortical atrophy (PCA)	Visuospatial as well as visuoperceptual abilities are affected. This may lead to visual inattention, known as Balint's syndrome. Impairments in arithmetic and reading, suggestive of dysfunction in the bilateral occipital and parietal cortices and visual streams
Corticobasal syndrome (CBS)	The condition is marked by Parkinsonian rigidity, myoclonus, apraxia of the eyes and limbs, cortical sensory impairments, and the phenomenon of an alien limb
Frontal variant of AD	Involves progressive behavioral changes such as apathy, loss of empathy, disinhibition, and occasionally compulsive behaviors or dietary changes. The dysexecutive-variant primarily affects executive function, including deficits in short-term memory and mental flexibility
Nonfluent primary progressive aphasia (nfPPA)	Characterized by difficulties in syntax, grammar, and buccofacial apraxia
Semantic variant primary progressive aphasia (svPPA)	Defined by semantic deficits, particularly in word comprehension. While most cases are linked to non-AD pathologies, a small proportion (16%) may be attributed to AD pathology
Copathologies (e.g., α-synuclein, TDP-43, and vascular pathology)	The presence of other neurodegenerative and vascular pathologies can influence AD's clinical presentation, often leading to more pronounced symptoms or variations in presentation. Copathologies complicate diagnosis. Biomarkers may help phenotype identification, or HPE of postmortem samples may help in differentiation



Figs 2A to D: (A) PET imaging normal FDG uptake in posterior cingulate gyrus; (B) Decreased FDG uptake in posterior cingulate gyrus suggestive of MCI; (C and D) Hypometabolism in parietotemporal and frontal areas suggestive of classical advanced AD

Table 4: Information about monoclonal antibodies and emerging research in AD[18]

Category	*Lecanemab (Leqembi)*	*Donanemab*	*Emerging research*
Type	Target-β-amyloid plaques	Target-β-amyloid plaques	Investigational drugs and studies on AD
Dosing regimen	10 mg/kg, given every 2 weeks (IV)	First three doses, 700 mg every 4 weeks, followed by 1400 mg every 4 weeks (IV)	Varies by drug (buntanetap, saracatinib, etc.)
Efficacy	30% reduction in clinical decline over 18 months (ADCOMS), 26% reduction in CDR-SB	15% reduction in clinical decline over 18 months (ADCOMS), 17% reduction in CDR-SB	Varies by study (early potential shown for some)
Safety	Infusion reactions, amyloid-related imaging abnormalities (ARIA)	Infusion-related reactions, ARIA	Safety concerns for each emerging drug
Key focus	Amyloid plaques reduction	Reduces amyloid plaques	Tau protein targeting, inflammation modulation, and insulin resistance

Clinical Alzheimer's Disease

In clinical AD, imaging provides critical information for confirming the diagnosis, assessing the extent of brain damage, and monitoring disease progression. Structural MRI is commonly used to evaluate brain atrophy, most commonly and early affected regions in AD are hippocampus and entorhinal cortex. In clinical AD, these regions show considerable shrinkage. PET scans continue to be valuable, as they can demonstrate widespread amyloid and tau deposition, which lead to the clinical manifestations of AD. FDG-PET also shows reduced metabolic activity in parietal and temporal lobes, which correlates with cognitive decline (Figs 2C and D). These imaging findings, in combination with cognitive assessments, help clinicians determine the stage of AD and predict disease progression.

Treatment—Recent Update

Existing FDA-approved medications primarily aim to alleviate symptoms rather than modify the disease course. As cholinergic deficiency has an important role in AD, cholinesterase inhibitors, such as donepezil, tacrine, rivastigmine, and galantamine, play an important role in the treatment of AD. Donepezil is a highly selective drug for acetylcholinesterase enzyme (AChE), rivastigmine inhibits reversibly both AChE and butyrylcholinesterase. Memantine (Namenda) regulates glutamate activity to improve memory and learning. These treatments are effective in the early and moderate stages of AD. Advanced research is going on in the development of therapies targeting the underlying mechanisms of AD Table 4.

Emerging research shows that ongoing studies are exploring various avenues, as follows:

- Tau protein targeting: Researchers are investigating tau aggregation inhibitors and vaccines to prevent the formation of tau tangles, another characteristic of AD.[17]
- Inflammation modulation: Increased levels of inflammatory markers, including C-reactive protein (CRP) and soluble receptors such as soluble receptor for advanced glycation end-products (sRAGE), have been detected in the CSF and blood of AD patients, highlighting the role of inflammation in the progression of the disease. Inflammation accelerates the deposition of Aβ and tau aggregates, creating a vicious cycle that amplifies neurodegeneration. Thus, targeting inflammation may be one of the preferred strategies in managing AD, although the complexity of the inflammatory response requires a nuanced approach.[19]
- Investigations into reducing chronic brain inflammation aim to protect neurons from damage. For instance, sargramostim (Leukine) is being studied for its potential to stimulate the immune system to clear harmful proteins.[20]
- Insulin resistance: Studies are examining how insulin resistance may affect brain function, with some trials testing insulin nasal sprays to slow AD progression. However, recent trials have not shown effectiveness.[21]
- Lifestyle modifications, such as regular exercise, healthy diet, and mental activities, are recommended to support brain health. Additionally, nonpharmacological interventions, including cognitive therapies and caregiver support programs, play a major role in reducing memory problems and improving quality of life.

Conclusion

Alzheimer's disease is a progressive condition of the brain, leading to a decline in cognitive function and memory. This

review emphasizes the significance of three main biomarker categories for AD diagnosis: (1) protein markers (Aβ, tau, and NFL), (2) miRNAs, and (3) noninvasive sources such as blood and saliva. Imaging techniques, particularly PET and MRI, play a pivotal role throughout the disease course of AD, from detecting early biomarkers in preclinical Alzheimer's disease (pre-AD) to assessing structural and functional brain changes in MCI and clinical AD. These imaging tools not only aid in diagnosis but also contribute to monitoring treatment efficacy and disease progression. While no cure currently exists, recent advancements in treatment strategies offer hope by targeting the disease pathology and improving memory as well as other cognitive domains. While challenges remain, the breakthroughs are happening in the AD treatment at a faster pace. One possible explanation for the limited success of clinical trials is that treatments are typically introduced at an advanced stage of the disease. Ongoing research into disease-modifying therapies and supportive care strategies offers hope for more effective interventions in the near future.

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