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BIOLOGICAL FLUID BIOMARKERS FOR ALZHEIMER'S DISEASE: A NARRATIVE REVIEW

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ABSTRACT

Background: Alzheimer's disease (AD), the leading cause of dementia, is characterized by amyloid beta (A β) plaques, tau tangles, and neuronal loss. Early diagnosis remains difficult, especially in prodromal phases. Biomarkers from biological fluids are critical for detecting pathology, aiding diagnosis, and monitoring progression.

Methods: This narrative review summarizes two decades of evidence on biological fluid biomarkers in AD, identified from PubMed, Scopus, and Web of Science using terms including "Alzheimer's disease," "biological fluid," "cerebrospinal fluid," "plasma," "serum," "urine," and "saliva." Studies included evaluated biomarkers with diagnostic or prognostic potential.

Results: Cerebrospinal fluid (CSF) biomarkers—A β 42, total tau (t-tau), and phosphorylated tau (p-tau)—are the most validated and form the basis of the AT(N) framework. Blood biomarkers have advanced with ultrasensitive assays; plasma p-tau isoforms (p-tau181, p-tau217, p-tau231) show high accuracy in distinguishing AD and correlate with PET imaging. Neurofilament light chain (NfL) in CSF and blood is a robust marker of neurodegeneration. Salivary, urinary, tear, and exosomal biomarkers remain experimental but promising due to their non-invasive collection.

Conclusion: Biological fluid biomarkers have transformed AD research and diagnosis. While CSF remains the reference standard, blood-based p-tau isoforms are emerging as scalable, non-invasive tools for early detection and monitoring. Broader clinical use will require assay standardization and integration into multimodal frameworks.

KEYWORDS

Alzheimer's disease; biomarkers; cerebrospinal fluid; blood biomarkers; plasma p-tau; neurofilament light chain; diagnosis; dementia.

MAIN ARTICLE

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that accounts for the majority of dementia cases globally (1). The disease is neuropathologically defined by extracellular accumulation of amyloid beta (A β) plaques, intracellular tau neurofibrillary tangles, and widespread neuronal degeneration. Clinically, AD presents with memory impairment, cognitive decline, and functional deterioration, ultimately leading to severe disability.

Despite decades of research, the definitive diagnosis of AD remains difficult in early stages, as symptoms often overlap with other dementias. Post-mortem histopathology has traditionally been the gold standard. However, in recent years, the development of biological fluid biomarkers has enabled in vivo detection of pathological processes, transforming both research and clinical practice .

Biological fluids such as cerebrospinal fluid (CSF), blood, saliva, urine, and exosomes carry proteins and metabolites that reflect underlying brain pathology. These biomarkers not only facilitate diagnosis but also hold potential for predicting disease progression, differentiating AD from other dementias, and monitoring therapeutic response. This narrative review synthesizes current evidence on biological fluid biomarkers in AD and evaluates their clinical utility and future prospects.

Methods

This article is structured as a narrative review. A literature search was conducted in PubMed, Scopus, and Web of Science databases, focusing on publications from 2000 to 2024. The search strategy used the terms "Alzheimer's disease," "biological fluid," "biomarkers," "cerebrospinal fluid," "blood," "plasma," "urine," and "saliva." Both original research and review articles were included if they addressed fluid biomarkers with diagnostic or prognostic relevance in AD. Studies limited to non-human models or methodological techniques without clinical application were excluded. References of included articles were also screened for additional sources.

Results

Cerebrospinal Fluid Biomarkers

CSF biomarkers are the most established in AD research. The core profile consists of reduced A β 42 (or A β 42/A β 40 ratio), elevated total tau (t-tau), and increased phosphorylated tau (p-tau, including p-tau181 and p-tau217). This triad reflects the hallmarks of amyloid deposition, tau pathology, and neurodegeneration, and is now embedded in the AT(N) classification system (2).

Additional CSF biomarkers include neurogranin, reflecting synaptic dysfunction; YKL-40, associated with astroglial activation and neuroinflammation; and neurofilament light chain (NfL), indicating axonal injury (3). These markers expand the understanding of AD beyond amyloid and tau pathology, although lumbar puncture as an invasive procedure limits widespread application.

Blood-Based Biomarkers

Blood biomarkers represent a major breakthrough due to their accessibility and potential for large-scale screening. Technological advances such as single molecule array (Simoa) and mass spectrometry have enabled accurate detection of low-abundance proteins.

Plasma A β 42/A β 40 ratios correlate with amyloid PET findings, but the greatest advances have come from plasma p-tau isoforms. Plasma p-tau181 and p-tau217 show high specificity for AD, while p-tau231 may be an early marker of preclinical pathology (4). Plasma NfL reflects neurodegeneration and correlates with disease severity but is not disease-specific. Collectively, these biomarkers provide a scalable and minimally invasive alternative to CSF.

Other Biological Fluids

Saliva, urine, tear fluid, and exosomes are being investigated as alternative biomarker sources. Salivary A β and tau species have been reported but with high variability across studies. Urinary oxidative stress markers such as isoprostanes may reflect systemic changes associated with AD. Tear fluid studies have identified tau and A β fragments, while exosomal biomarkers, enriched with neuron-derived proteins, offer a novel method to capture central

pathology from peripheral fluids (5). These approaches remain experimental but hold promise for future applications.

Integrative Approaches

AD is a multifactorial disease, and no single biomarker fully captures its complexity. Integrative approaches combining CSF or blood biomarkers with imaging, genetic, and cognitive measures are increasingly used to enhance diagnostic accuracy. Machine learning models incorporating multiple biomarker panels are also being developed for patient stratification and prediction of disease progression (6).

Table 1 : Overview of Major Biological Fluid Biomarkers for Alzheimer's Disease

Biomarker Type	Examples	Biological Process	Clinical Utility	Limitations
CSF Biomarkers	A β 42, A β 42/A β 40, t-tau, p-tau181, p-tau217	Amyloid, tau, neurodegeneration	Gold standard; integrated into AT(N) framework	Invasive; not suitable for screening
Blood Biomarkers	Plasma A β 42/A β 40, p-tau181, p-tau217, NfL	Amyloid, tau, axonal injury	Minimally invasive; scalable; correlates with PET	Standardization needed; confounders
Emerging CSF	Neurogranin, YKL-40, NfL	Synaptic dysfunction, inflammation	Early detection; complementary markers	Validation required
Salivary Biomarkers	A β , tau species	Amyloid and tau pathology	Non-invasive; repeatable	Inconsistent results
Urinary Biomarkers	Isoprostanes, clusterin	Oxidative stress, systemic markers	Low-cost; non-invasive	Non-specific; variable findings
Exosomal Biomarkers	Neuronal exosomal A β , tau	Neuronal cargo across BBB	Potentially specific and mechanistic	Complex isolation; early-stage research

Discussion

The emergence of biological fluid biomarkers has transformed the diagnostic landscape of Alzheimer's disease. CSF biomarkers are highly validated and continue to serve as the gold standard, accurately reflecting amyloid and tau pathology as well as neurodegeneration. Their integration into international diagnostic frameworks underscores their reliability. Yet, limitations of lumbar puncture, including invasiveness and patient acceptability, prevent their use in routine population screening (7).

Blood-based biomarkers are rapidly advancing and may overcome these barriers. Plasma p-tau isoforms have shown excellent performance in distinguishing AD from other dementias and in predicting amyloid and tau PET status. Plasma NfL, while less specific, is a valuable marker of neurodegeneration and disease progression (3). These markers provide opportunities for early detection, repeated monitoring, and large-scale screening in both clinical and research contexts. However, challenges such as assay variability, pre-analytical influences, and the need for international standardization must be addressed before they can be implemented widely.

Other fluids, including saliva, urine, and exosomes, remain experimental but highlight the ongoing search for non-invasive diagnostic tools (5). Their role in future diagnostics will depend on reproducibility and validation in large, diverse populations. Exosomes, in particular, offer an innovative approach to detect neuron-derived proteins in peripheral blood, potentially bridging the gap between central and peripheral pathology.

Beyond single markers, integrative strategies combining fluid biomarkers with imaging, genetics, and cognitive assessments will likely yield the most clinically relevant outcomes. Such approaches are particularly valuable for patient stratification in clinical trials, monitoring therapeutic responses, and enabling precision medicine. The growing development of disease-modifying therapies further increases the importance of scalable biomarkers to identify eligible patients and track treatment efficacy.

Overall, fluid biomarkers represent one of the most important advances in AD research. Continued progress requires harmonization of methods, ethical consideration in the disclosure of results, and validation across diverse populations. These steps will ensure that biomarkers move from research into routine clinical use, ultimately improving patient care and outcomes.

Conclusion

Biological fluid biomarkers have become essential tools in Alzheimer's disease research and diagnosis. CSF biomarkers remain the most reliable indicators of pathology, but blood-based biomarkers, especially plasma p-tau isoforms, are emerging as transformative, non-invasive, and scalable alternatives. Other biological fluids, while promising, are still under investigation. The integration of biomarkers into multimodal frameworks, alongside standardized methodologies, will be critical for their translation into clinical practice. These advances have the potential to enable earlier detection, improve differential diagnosis, and support the development of effective disease-modifying therapies.

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