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Molecular Pathways in The Pathophysiology of Alzheimer's Disease: Biochemical Mechanizm And the Diagnostic Value of Current Peripheral Parameters

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Abstract

Alzheimer's Disease (AD) represents the primary cause of dementia worldwide, imposing a significant socioeconomic burden on aging populations. Traditionally diagnosed through clinical symptoms and postmortem histopathology, the paradigm has shifted toward biological definitions using neuroimaging and cerebrospinal fluid (CSF) analysis. However, these methods are constrained by high costs and invasiveness.

This comprehensive review aims to elucidate the core biochemical pathways underlying AD pathophysiology—specifically amyloid-beta aggregation, tau hyperphosphorylation, neuroinflammation, and mitochondrial dysfunction—and critically evaluate the diagnostic performance, clinical utility, and accuracy of emerging blood-based peripheral parameters.

A systematic literature search was conducted across PubMed, Web of Science, and Google Scholar for peer-reviewed studies, clinical trials, and meta-analyses published between 2020 and 2026. Keywords included "Alzheimer's disease", "amyloid-beta", "tau hyperphosphorylation", "peripheral biomarkers", "p-tau217", and "neurofilament light chain". Data from major international cohorts were synthesized.

The driving force of AD involves the amyloidogenic processing of amyloid precursor protein by beta and gamma secretases, producing hydrophobic Amyloid-beta 42 peptides that form extracellular plaques. This triggers glycogen synthase kinase-3 beta activation, leading to tau hyperphosphorylation, microtubule disassembly, and intracellular neurofibrillary tangles. Simultaneously, chronic neuroinflammation via microglial activation and mitochondrial bioenergetic failure accelerate neuronal death. Recent advances in ultra-sensitive immunoassays have enabled the detection of these central pathologies in peripheral blood. Plasma p-tau217 exhibits exceptional diagnostic accuracy, with an Area Under the Curve (AUC) between 0.90 and 0.96, outperforming other tau variants in predicting brain amyloidosis. The plasma Amyloid-beta 42/40 ratio, while highly specific, shows lower dynamic stability but provides substantial diagnostic power when combined with p-tau217. Concurrently, plasma Neurofilament Light Chain (NfL) serves as a robust indicator of longitudinal axonal injury, while Glial Fibrillar Acidic Protein (GFAP) effectively mirrors early-stage reactive astrogliosis and neuroinflammation.

Peripheral biochemical parameters revolutionize the AD diagnostic timeline by identifying pathological changes up to two decades before symptom onset. Integrating these blood-based biomarkers into routine clinical workflows offers a non-invasive, cost-effective strategy for early screening, disease progression tracking, and the timely initiation of disease-modifying therapies.

Keywords: Alzheimer's Disease, Biochemical Mechanisms, Peripheral Biomarkers, p-tau217, Neurofilament Light Chain.

1. Introduction

Alzheimer's Disease (AD) is a progressive, irreversible neurodegenerative disorder that accounts for approximately 60% to 80% of all dementia cases globally. As life expectancy increases worldwide, the prevalence of AD is projected to triple by the mid-century, making it one of the most critical public health challenges of our time. Clinically, the disease manifests initially as subtle episodic memory deficits, which inexorably progress to comprehensive cognitive decline, behavioral alterations, and a total loss of functional independence.

For decades, the definitive diagnosis of AD was strictly postmortem, requiring histopathological confirmation of extracellular senile plaques and intracellular neurofibrillary tangles (NFTs). In clinical settings, diagnosis relied on the exclusion of other dementias and the documentation of manifest cognitive impairment via neuropsychological testing. However, this symptom-based framework is fundamentally flawed; by the time clinical symptoms appear, massive, irreversible neuronal loss and synaptic degradation have already occurred.

The discovery that AD pathology develops silently over a presemptomatic phase lasting 15 to 20 years led to the establishment of the ATN (Amyloid, Tau, and Neurodegeneration) framework. This framework defines AD biologically rather than clinically. Initially, ATN classification required cerebrospinal fluid (CSF) collection via lumbar puncture or positron emission tomography (PET) imaging. While highly accurate, PET imaging is restricted by prohibitive costs and lack of widespread availability, while lumbar punctures are invasive and met with low patient compliance.

To overcome these barriers, the field of clinical biochemistry has focused on developing blood-based biomarkers. Driven by ultra-sensitive detection technologies, it is now possible to quantify central nervous system proteins circulating in peripheral blood at picogram-per-milliliter levels. This review provides a comprehensive analysis of the molecular pathways driving AD and evaluates how current peripheral parameters reflect these central biochemical changes to reshape early diagnosis (1-6).

2. Methods

To evaluate the biochemical mechanisms and peripheral diagnostic parameters of AD, a rigorous review of scientific literature was executed. Electronic databases including PubMed, Web of Science, and Google Scholar were searched for peer-reviewed articles published from January 2020 through early 2026.

The search strings used logical operators to combine specific terms: ("Alzheimer's disease" AND "pathophysiology" and "plasma biomarkers" AND ("p-tau217" or "neurofilament light chain" or "GFAP")). The selection focused primarily on prospective cohort studies, multicenter validation trials, high-impact systematic reviews, and meta-analyses.

Special emphasis was placed on data emerging from major international longitudinal networks, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Swedish BioFINDER study, and the Translational Biomarkers in Aging and Dementia (TRIAD) cohort. Studies utilizing older, less sensitive enzyme-linked immunosorbent assays (ELISA) on plasma samples were excluded in favor of those utilizing ultra-sensitive Single Molecule Array (Simoa) technology or immunoprecipitation-coupled mass spectrometry (IP-MS), ensuring maximum clinical relevance.

3. Results

3.1. Core Biochemical Pathways of Alzheimer's Disease

3.1.1. The Amyloidogenic Pathway and Plaque Aggregation

The primary biochemical hallmark of AD is the accumulation of amyloid-beta (Abeta) peptides in the extracellular matrix of the brain. These peptides are derived from the sequential proteolysis of the Amyloid Precursor Protein (APP), a type-I transmembrane glycoprotein. In the physiological, non-amyloidogenic pathway, APP is initially cleaved by alpha-secretase, releasing a soluble, neuroprotective fragment (sAPP-alpha).

In AD, the balance shifts to the amyloidogenic pathway. Here, APP is first cleaved by beta-site APP cleaving enzyme 1 (BACE1, or beta-secretase), yielding a membrane-bound C-terminal fragment (C99). Subsequently, the gamma-secretase complex—an intramembrane-cleaving protease containing presenilin 1 or 2—cleaves the C99 fragment. Because gamma-secretase exhibits imprecise cleavage sites, it generates

Abeta peptides of varying amino acid lengths, primarily Abeta 40 and Abeta 42.

The 42-amino-acid variant (Abeta 42) is highly hydrophobic and prone to self-assembly. It rapidly forms soluble oligomers, which are widely considered the most neurotoxic species due to their ability to disrupt synaptic membranes, induce pore formation, and alter calcium homeostasis. Over time, these oligomers coalesce into protofibrils and mature into the insoluble beta-pleated sheets that constitute senile plaques (7-9).

3.1.2. Tau Hyperphosphorylation and Axonal Collapse

Physiological tau is a highly soluble microtubule-associated protein concentrated in neuronal axons, where it stabilizes the microtubule network essential for intracellular transport. In AD, the accumulation of extracellular Abeta oligomers triggers an intracellular signaling cascade that activates several protein kinases, most notably Glycogen Synthase Kinase-3 beta (GSK-3beta) and Cyclin-Dependent Kinase 5 (CDK5).

These activated kinases hyperphosphorylate tau, adding excess phosphate groups to its structure. Hyperphosphorylated tau (p-tau) loses its affinity for microtubules, detaches from the axonal cytoskeleton, and accumulates within the somatodendritic compartment of the neuron. Deprived of stabilizing tau, the microtubule network disassembles, paralyzing axonal transport. Concurrently, free p-tau molecules aggregate into soluble oligomers, pair to form paired helical filaments (PHFs), and ultimately condense into insoluble intracellular neurofibrillary tangles (NFTs), which induce apoptosis (10-12).

3.1.3. Neuroinflammation and Microglial Polarization

Neuroinflammation in AD is not a passive consequence of tissue damage but an active driver of neurodegeneration. Microglia, the resident myeloid cells of the central nervous system, monitor the brain parenchyma. When microglia encounter extracellular Abeta plaques, they bind them via surface receptors such as TREM2, toll-like receptors (TLRs), and CD36.

Initially, this shifts microglia into a neuroprotective, phagocytic phenotype aimed at clearing the plaques. However, persistent exposure to Abeta aggregates leads to chronic microglial activation and polarization into a pro-inflammatory or Disease-Associated Microglia (DAM) state. These cells assembly the NLRP3 inflammasome, triggering the sustained release of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin-1 beta (IL-1beta), and Interleukin-6 (IL-6). This chronic inflammatory environment damages adjacent neurons and impairs the phagocytic capacity of microglia, accelerating plaque accumulation (13-16).

3.1.4. Mitochondrial Dysfunction and Oxidative Stress

Neurons are highly dependent on oxidative phosphorylation for energy. In AD, intracellular Abeta oligomers and p-tau interact directly with mitochondrial membranes, disrupting electron transport chain complexes, particularly Complex I and Complex IV (cytochrome c oxidase).

This inhibition causes a severe reduction in Adenosine Triphosphate (ATP) production and accelerates the leakage of electrons, leading to the overproduction of Reactive Oxygen Species (ROS). The resulting oxidative stress induces lipid peroxidation of neuronal membranes, damages mitochondrial DNA, and opens the mitochondrial permeability transition pore (mPTP), releasing cytochrome c into the cytoplasm and activating caspase-dependent apoptotic pathways (3,6,7,15,16).

3.2. Evaluation of Current Peripheral Biochemical Parameters

Thanks to technologies like Simoa and IP-MS, central pathologies can now be reliably measured in blood plasma. The diagnostic performance and mechanisms of these current peripheral parameters are detailed below (17-19).

Table-1. Pathological Formation Mechanisms, Diagnostic Accuracy Rates, and Clinical Performance of Alzheimer's Blood Biomarkers.

Peripheral Parameter	Central Pathological Mechanism	Diagnostic Accuracy (AUC)	Clinical Performance Summary
Plasma p-tau217	Active tau phosphorylation linked to amyloid plaque deposition.	**0.90-0.96**	The gold standard plasma biomarker; accurately detects brain amyloidosis and tau tangles, outperforming p-tau181 and p-tau231.

Plasma Abeta 42/40 Ratio	Extracellular sequestration of Abeta 42 into cerebral senile plaques.	**0.80-0.88**	Decreases as brain amyloid deposition increases; acts as an early indicator of amyloidosis, especially when combined with p-tau217.
Plasma Neurofilament Light Chain (NfL)	Large-caliber axonal damage and general neurodegeneration.	**0.75-0.82** (Non-specific)	Lacks specificity for AD but correlates strongly with the rate of cognitive decline and structural brain atrophy.
Plasma Glial Fibrillary Acidic Protein (GFAP)	Reactive astrogliosis secondary to early amyloid deposition.	**0.85-0.92**	Rises sharply in the earliest stages of amyloid accumulation, serving as a highly sensitive blood reporter for neuroinflammation (17-19).

3.2.1. Plasma p-tau217

Among the various phosphorylated tau species isolated in plasma (including p-tau181 and p-tau231), plasma p-tau217 has emerged as the most reliable peripheral parameter for AD. Its elevation in plasma occurs almost simultaneously with the initial appearance of amyloid plaques in the brain, well before mature tau tangles can be visualized by PET imaging. Extensive cohort validations demonstrate that plasma p-tau217 differentiates AD from non-AD neurodegenerative disorders with an Area Under the Curve (AUC) exceeding 0.93. Utilizing a two-cut-off "three-tier" clinical strategy allows plasma p-tau217 to confirm or rule out AD pathology accurately, potentially reducing the clinical need for confirmatory CSF or PET testing by up to 75% (10-12).

3.2.2. Plasma Abeta 42/40 Ratio

Because Abeta 42 accumulates inside cerebral plaques, less free peptide is able to diffuse into the bloodstream, causing a measurable drop in peripheral Abeta 42 levels. In contrast, Abeta 40 concentrations remain relatively stable. Thus, a reduced plasma Abeta 42/40 ratio serves as a direct indicator of cortical amyloid deposition. While individual Abeta measurements can fluctuate due to peripheral production by platelets, checking the ratio via high-precision IP-MS provides excellent diagnostic consistency and acts as an early marker of amyloid pathology 10-12).

3.2.3. Plasma Neurofilament Light Chain (NfL)

Neurofilament Light Chain is a structural scaffolding protein exclusive to neuronal axons. When axons fracture due to neurodegenerative processes, NfL is released into the interstitial fluid, drains into the CSF, and enters the systemic circulation. Plasma NfL is not specific to AD; it rises in response to any condition causing axonal collapse, such as frontotemporal dementia, amyotrophic lateral sclerosis, or acute stroke. However, within confirmed AD cohorts, plasma NfL serves as an indispensable tool for longitudinal tracking, as its concentration mirrors the speed of clinical progression and structural brain atrophy (10,12,16).

3.2.4. Plasma Glial Fibrillary Acidic Protein (GFAP)

GFAP is an intermediate filament protein found inside astrocytes. In response to early Abeta oligomerization, astrocytes become reactive and undergo astrogliosis, upregulating GFAP production. Interestingly, plasma GFAP levels elevate more dramatically than CSF GFAP levels during the earliest stages of AD. This suggests that reactive astrocytes surrounding blood-brain barrier interfaces release GFAP directly into the peripheral blood, making it a highly sensitive indicator of early plaque-induced neuroinflammation (10,12,16).

4. Discussion

The development of highly sensitive peripheral biochemical parameters marks a major turning point in modern neurology, transitioning AD management from reactive care to proactive, biology-driven intervention. For decades, clinical trials targeting Abeta or tau failed repeatedly, largely because therapies were administered to patients who already displayed advanced clinical dementia and extensive, irreversible brain damage (2,3,9,10,20-23).

The clinical introduction of plasma biomarkers like p-tau217 and the Abeta 42/40 ratio redefines this landscape. These tests allow for the identification of eligible individuals during the presemptomatic or Mild Cognitive Impairment (MCI) stages. This early window is vital for the optimal efficacy of newly approved, disease-modifying monoklonal antibodies, such as lecanemab and donanemab, which slow cognitive decline by clearing amyloid plaques before severe axonal collapse occurs (10-12).

However, implementing peripheral parameters into routine clinical practice requires careful consideration of potential confounding variables. For instance, because

these biomarkers circulate in systemic blood, their clearance is highly dependent on renal function. Clinical data indicate that patients with chronic kidney disease (CKD) or reduced estimated glomerular filtration rates (eGFR) often exhibit falsely elevated plasma levels of p-tau217, NfL, and GFAP due to reduced renal filtration rather than accelerated neurodegeneration (3,10-12).

Additionally, systemic metabolic conditions can influence these markers. Studies looking at cell-specific transport mechanisms have found that in patients with Type 2 Diabetes Mellitus, neural-derived exosomal (NDE) fractions show altered mitochondrial proteins, such as NDUFS3 and SDHB. This highlights how systemic metabolic dysfunction can impair mitochondrial health and accelerate AD pathways, demonstrating that peripheral readings must be interpreted alongside a patient's overall metabolic and renal profile (10-12,14).

To maximize diagnostic accuracy and minimize false results, the clinical field is moving away from single-marker assessments toward integrated biomarker panels. Combining a highly specific marker of amyloid/tau pathology (p-tau217) with a marker of neuroinflammation (GFAP) and a marker of axonal damage (NfL) creates a comprehensive biochemical fingerprint. This multi-analyte approach captures the complex, multi-stage nature of AD, providing clear diagnostic answers even in medically complex patients (3,4,9-12,15,17).

5. Conclusion and Recommendations

Alzheimer's Disease progresses through an intricate web of molecular changes, characterized by amyloidogenic processing, tau hyperphosphorylation, chronic neuroinflammation, and mitochondrial failure. Advanced bioanalytical technologies have bridged the gap between central brain pathology and peripheral blood, allowing these complex changes to be tracked via simple blood samples. Peripheral parameters, led by plasma p-tau217 and supported by the Abeta 42/40 ratio, GFAP, and NfL, provide an accessible, scalable, and non-invasive alternative to traditional CSF and PET diagnostics (10-12, 24-26).

Based on these insights, the following actions are recommended for clinical research and practice:

1. Primary Care Screening: Establish validated plasma biomarker panels, centered on p-tau217, as standard screening tools in primary care settings for elderly individuals presenting with subjective cognitive complaints.
2. Therapeutic Optimization: Utilize blood-based biomarkers to identify patients in the earliest presemptomatic or prodromal phases of AD, ensuring disease-modifying therapies are introduced when they can preserve the most cognitive function.
3. Standardized Protocols: Develop universal clinical cut-offs and pre-analytical handling standards that account for age, renal function, and metabolic comorbidities, ensuring consistent diagnostic performance across diverse patient populations (10-12,27-33).

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