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Early Diagnosis of Alzheimer's Disease with Blood Test; Tempting but Challenging

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ABSTRACT

The increasing prevalence of Alzheimer's disease (AD) has led to a health crisis. According to official statistics, more than 55 million people globally have AD or other types of dementia, making it the sixth leading cause of death. It is still difficult to diagnose AD and there is no definitive diagnosis yet; post-mortem autopsy is still the only definite method. Moreover, clinical manifestations occur very late in the course of disease progression; therefore, profound irreversible changes have already occurred when the disease manifests. Studies have shown that in the preclinical stage of AD, changes in some biomarkers are measurable prior to any neurological damage or other symptoms. Hence, creating a reliable, fast, and affordable method capable of detecting AD in early stage has attracted the most attention. Seeking clinically applicable, inexpensive, less invasive, and much more easily accessible biomarkers for early diagnosis of AD, blood-based biomarkers (BBBs) seem to be an ideal option. This review is an inclusive report of BBBs that have been shown to be altered in the course of AD progression. The aim of this report is to provide comprehensive insight into the research status of early detection of AD based on BBBs.

Keywords: Alzheimer's disease; blood-based biomarker; early diagnosis; multiplexing

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The challenge of Alzheimer's disease diagnosis

There is no doubt that Alzheimer's disease (AD) is among the health priorities nowadays, especially in developed countries. According to latest World Health Organization (WHO) report, more than 55 million people worldwide have AD or other types of dementia and the number of new cases is about 10 million per year, although only one fourth of them have been diagnosed (1); a challenge that has turned AD into a health crisis, i.e. belated and uncertain diagnosis. Despite remarkable advances in diagnosis with up to 90% accuracy, there is no single and definite test to detect AD yet, and autopsy is still the only definitive method (2). Physicians need to assess several factors to confirm AD with more certainty including medical history and brain imaging, in addition to physical, neurological and mental status exams (genetic testing also can be done in the case of familial AD), while the differentiation of AD among other causes of dementia is still challenging (3). Clinical diagnostic guidelines undergo revision time to time according to recent scientific discoveries.

It is well recognized that AD starts at the molecular level many years, or even decades (20 years or more), prior to clinical manifestations (4). Therefore, profound irreversible changes have already occurred at the time of diagnosis (5). There are different stages proposed for the AD; from No Cognitive Impairment (NCI) to dementia. In the reports of a consensus panel of experts from the US and Europe regarding the improvement of AD diagnosis guidelines, it has been proposed to consider the second phase of disease (Subjective Cognitive Impairment (SCI)) as preclinical AD, before Mild Cognitive Impairment (MCI) and dementia phases (6). In this preclinical stage, changes in some biomarkers are measurable prior to any neurological damage or clinical manifestation. Incorporation of underlying biomarkers in diagnosis protocol, including the biomarkers of A-β accumulation, the biomarkers of neuronal degeneration or injury, along with imaging data, was another point stated in these reports (7).

Late indication of AD seems to be one of the main reasons of failure in effective treatment (8). Hence, creating a reliable, fast, and affordable method capable of detecting AD in early stage is of utmost importance. Vast endeavor is being done to find a new way of diagnosis at earlier stages based on novel AD biomarkers. In this regard, multiple biomarker categories are assumable including imaging, genetic, cerebrospinal fluid (CSF) and blood-based biomarkers, ocular and olfactory signals (visual and olfactory dysfunctions due to the impairment of neural networks) (9, 10), and very recently, digital biomarkers, which are defined as physiological and behavioral data that are collected and assessed non-invasively by means of mobile and wearable technologies (11); of these some are being evaluated in clinical trials (12).

Among these, peripheral biomarkers, e.g., blood-based ones are extensively under investigation and some of them are really promising. Being much easier to attain with considerably lower cost and difficulty for patients, and possibility of multiple sampling compared with other categories, blood-based biomarkers (BBBs) are an ideal option.

According to the literature, a high number of biomarkers have been shown to change in the plasma/serum/whole blood during neurodegeneration process as reported in tables 1-9. These biomarkers belong to various categories of biomolecules possessing different physiological functions. In this review, we provide a categorized comprehensive report of BBBs that have shown to be altered in AD or MCI patients.

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We aim to provide readers a comprehensive insight of research status in early detection of AD based on BBBs.

Classification of Blood-Based Biomarkers (BBBs) of AD

A major challenge in utilizing BBBs for early detection of AD is the selection of a reliable biomarker or a combination of them (multiplex) that can show acceptable accuracy and precision. So far, several molecular mechanisms have been introduced for AD pathogenesis, such as amyloid β hypothesis, tau protein pathogenesis, cholinergic or glutamatergic neurotransmission pathways, the theory with emphasis on autophagy and the role of inflammatory processes, and oxidative stress (13, 14). In addition, neurodegeneration and cell loss leads in expression of biomarkers associated with cell-death including apoptosis biomarkers (15). These different proposed hypotheses with several involved molecules make a great chance for discovering potential AD biomarkers (Figure 1). Various methods, including immunoassays, omics technology, and nano-based techniques, have been employed to identify either a single biomarker or a multiplex of biomarkers to date. The authors intend to assess and discuss these techniques in a separate paper.

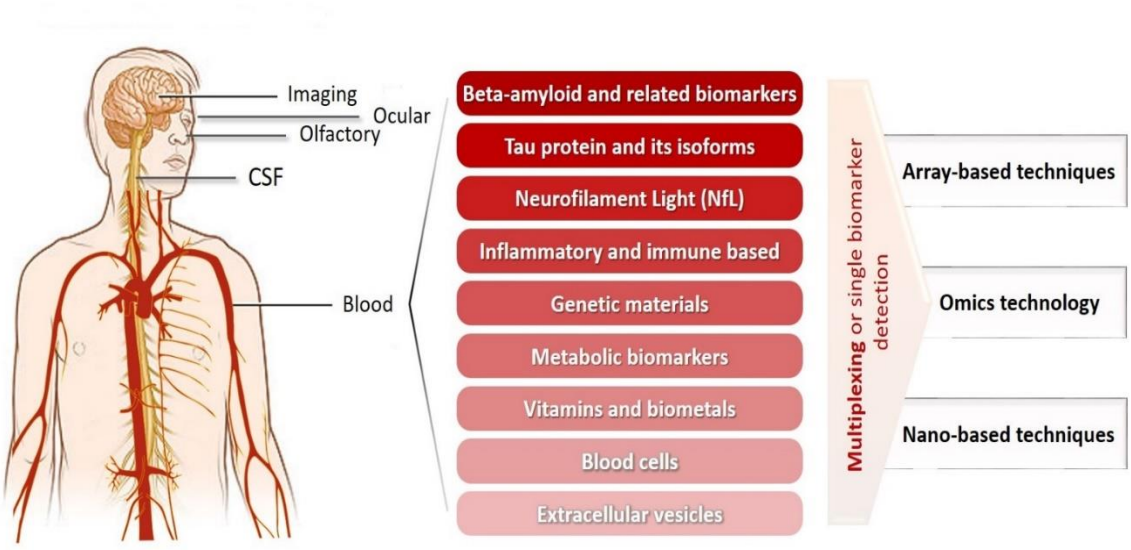

Fig.1. Alzheimer's disease biomarkers.

Beta-amyloid and Related Biomarkers

Although the theory of the role of β-amyloid protein in AD development is old, its application in early diagnosis is not. β-amyloid is perhaps the first and the main protein found to be associated with the conversion of MCI to AD (16). The Food and Drug Administration (FDA) approval of aducanumab, Aβ- monoclonal antibody, for the early AD treatment have encouraged the theory (17). Considering the results of numerous studies that have proved the role of β-amyloid in development and progression of AD, β-amyloid protein is suggested as one of the diagnostic entities in the updated framework of NIA-AA (National Institute on Aging and Alzheimer's Association), in which the AD diagnostic criteria have been shifted from clinical manifestation to a biological definition (18).

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Amyloid precursor protein (APP) cleaves into various isoforms mainly $A\beta_{1-40}$ ($A\beta_{40}$) and $A\beta_{1-42}$ ($A\beta_{42}$). In healthy individuals, the first one is more abundant than the latter one (about 70% vs. 15%) (19). The abnormal cleavage of APP is known to form excessive insoluble $A\beta_{42}$, which aggregates in the brain in forms of oligomers, protofibrils, and fibrils. In early stage of AD, the elevation of these insoluble oligomers is the main reason of synaptic destruction (20).

Evidence has shown the abnormality of β-amyloid CSF levels in the earliest stages of AD (21). It is presumed that sequestration of β-amyloid inside the amyloid plaques decreases the amount of it in CSF. This is often observed several years before manifestation of clinical symptoms (22, 23). Although various amounts have been reported, about 50% reduction in $A\beta_{42}$ CSF level is considered as one part of the "AD signature" (24, 25).

The specificity of CSF-$A\beta_{42}$ was reported to be about 82% for discrimination of AD from healthy individuals, and about 67% for discrimination of AD from other types of dementia (26). These data varied from study to study leading to the general concept that $A\beta_{42}$ alone is not accurate for detection of AD. Some studies investigated the ratio of $A\beta_{42}/A\beta_{40}$ and vice versa (27). It is found that the CSF $A\beta_{42/40}$ ratio could be correlated to the amyloid amount detected in the brain tissue by PET in the following 2-5 years (28).

It is now recognized that the only source of β-amyloid is not the brain itself. Peripheral β-amyloid originates from various tissues and body organs including, but not limited to, platelets, other blood cells, kidney, liver, and muscles. It has recently been shown that circulating β-amyloid can pass blood-brain barrier and may play an important role in AD pathologies (14, 29). Wang *et al*. have extensively reviewed the crosstalk between peripheral and central β-amyloid and their role in β-amyloid production and clearance (30).

Contrary to CSF level, as shown in table 1, plasma concentration of β-amyloid may not change in one direction, which could make it inconclusive. One of the reasons for this discrepancy might be due to the relatively low concentration of β-amyloid protein in plasma, which makes it difficult to be accurately quantified. Numerous detection methods have been developed so far to overcome this limitation offering various ranges of specification (31-33). Thanks to the development of more sensitive techniques, currently, $A\beta_{42}/A\beta_{40}$ is among the promising diagnostic plasma biomarkers along with p-tau217, p-tau181, and neurofilament light (NfL) (34).

To determine the early changes leading to AD, scientists took a step backward to investigate the process that results in creation of these two β-amyloid isoforms. Hence, studies were extended to the evaluation of various peptides, enzymes or genes involved in this pathway (35). The proteolysis of APP takes place by α- or β-secretase enzymes, which is subsequently followed by γ-secretase cleavage. Presenilins are components of multiprotein γ-secretase. It is presumed that the overexpression or mutation of β- or γ-secretases or presenilins could lead to AD (36, 37), however, the protective or pathological effects of α- and β-secretases or the APP intracellular domain peptide (AICD) fragments generated by γ-secretase are not defined clearly yet (38). Apart from β-amyloid peptides, APP, β-secretase (BACE), γ-secretase and AICD are among the β-amyloid relevant compounds which have been investigated the most (17). Table 1 summarizes the studies on β-amyloid and its related AD biomarkers in plasma.

Tau Protein and its Isoforms

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The second main hallmark of AD is Tau pathology. Tau protein is predominantly found inside neurons. Stabilization of microtubules is one of the important functions of this protein. Tau, a member of microtubule-associated proteins family, consists of at least 30 phosphorylation sites. In pathological situations, specific tau phosphorylation increases its ability for self-assembly. In AD, the formation of β-amyloid aggregates, stimulates several kinases leading to the hyper-phosphorylation of tau protein which eventually forms neurofibrillary tangles (NFTs) (64).

Table 1. AD biomarkers related to β-Amyloid theory.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ Aβ40 in plasma (~1.2-fold, p=0.005) ↔ Aβ42 in plasma	78 probable AD & 61 controls	Sandwich ELISA	(39)
↓ Aβ40 in plasma ↔ Aβ42 in plasma	363 Dementia & MCI (from total 1045, 70-Year-Old men) & 196 Dementia & MCI (from total 680, 77-Year-Old men)	BNT77 ELISA	(40)
↓ Aβ40 in plasma ↓ Aβ42 in plasma	Swedish BioFINDER center: 513 CU & 265 MCI & 64 AD German Biomarker center: 34 CU & 109 MCI & 94 AD	Elecsys Immunoassays	(28)
↔ Aβ40 in plasma ↓ Aβ42 in plasma ↑ Aβ40/Aβ42 ratio in plasma ↔ APP 669–711 isoform in plasma ↑ (APP 669–711)/Aβ42 in plasma	NCGG study (n=121) AIBL study (n=252) balanced number of CU, MCI, AD	IP–MS with MALDI–TOF mass spectrometry	(41)
↔ Aβ40 in plasma (increase with age and familial AD, neither sensitive nor specific for MIC or sporadic AD)	146 sporadic AD, 37 MIC, 96 PD, 92 control	BNT77 Sandwich ELISA	(42)
↔ Aβ40 in plasma	28 sporadic probable AD, 40 neurologic patients without dementia, 25 controls	ELISA	(43)
↑ Aβ42 in plasma (in familial AD and in 10-20% of sporadic AD cases)	Study1: 12 Carrier & 31 non carrier of APP mutation Study2: 9 carrier PS1 mutation, 3 carrier PS2 mutation, 1 carrier APP mutation and 14 control Study3: 71 elderly patient & 75 control	BAN50/BA27 and BAN50/BC-05 sandwich ELISA	(44)
↑ Aβ42 in plasma (p= 0.002)	105 CU & 64 AD	Double-antibody sandwich- ELISA	(45)
↑ Aβ42 in plasma	128 participants (mutation carriers vs. non-carriers)	INNO-BIA Multiplex Assay, Innogenetics	(46)
↑ Aβ42 in plasma (p=0.01) ↑ Aβ42/ Aβ40 ratio in plasma (p=0.001)	20 CU mutation carriers, 24 CU non-carriers (18-26 years old - matched for gender, age, educational level)	Multiplex Assay (Luminex xMAP bead-based methods (INNO-BIA AlzBio3™))	(47)
↑ Aβ42 in plasma (p=0.031)	17 cases at risk for presenilin-1 and 4 cases at risk of amyloid precursor protein mutation	Sandwich ELISA	(48)
↔ Aβ42 in plasma (p=0.079)	28 AD, 13 MCI, 6 CU (Taiwanese)	Immunoassays	(49)

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Table 1. AD biomarkers related to β-Amyloid theory.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↔ Total β amyloid in plasma (p=0.409)			
↔ Aβ42 in plasma	28 sporadic probable AD, 40 neurologic patients without dementia, 25 CU	ELISA	(50)
↑ Pathogenic Aβ in plasma (↑ β-sheet content and shift of amide I band to lower wavenumbers, sensitivity: 90%)	39 AD & 61 control	Immuno-infrared sensor (Aβ secondary structure)	(51)
↑ Aβ42/Aβ40 in plasma	435 CU (follow-up for a median of 5 years)	Elecsys Immunoassays	(52)
↓ Aβ42/ Aβ40 ratio in plasma (No significant alteration with ELISA but significant differences via the INNO-BIA plasma Aβ assay, p= 0.001)	724 CU, 122 MCI, 186 AD	Commercial multiplex assay & ELISA	(53)
↓ APPsβ isoform in plasma ↔ APPsα isoform in plasma	80 probable AD, 14 bvFTD, 36 control	ELISA	(54)
↑ APP (115 KD/β-actin) in platelets (1.9-fold, p=0.0001) ↓ APP (130/105 KD) in platelets (0.57-fold, p=0.0012)	30 MCI/AD, 23 normal control	ELISA & western blot	(55)
↓ APP (130/105 KD) in platelets (~0.5-fold for mAD & vmAD, p<0.001 - ~0.7-fold for MCI, p<0.001)	35 mAD, 21 vmAD, 30 MCI, 25 control	Immunoblotting	(56)
↔ BACE1 in plasma (p = 0.41) ↓ BACE1 in platelets (0.88-fold, p=0.03)	15 AD & 12 CU	ELISA	(57)
↓ Anti-amyloid antibodies in serum (0.4-fold, p<0.02)	39 AD & 39 CU	ELISA	(58)
↓ Anti-amyloid antibodies in serum	Study 1: 39 AD & 39 controls Study 2: 19 E4-negative AD & 33 E4-negative controls	ELISA	(59)
↓ Anti-amyloid antibodies in serum (p=0.001, independent of age, cognitive status, and ApoEε4 carrier status)	96 AD &30 CU	Immunoassay	(60)
↑ ALZAS in plasma ↑ALZAS antibody in serum (up to 10-fold)		ELISA	(61-63)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), APP (Amyloid precursor protein), bvFTD (behavioral variant frontotemporal dementia), mAD (mild Alzheimer's disease), vmAD (very mild Alzheimer's disease), BNT77 (IgA anti- Aβ 11-28), PD (Parkinson disease), BACE (β-secretase), ALZAS (Alzheimer's Associated protein, a novel gene/protein with a 79 amino acid sequence, containing Aβ-42 fragment, APP transmembrane signal and a 12 amino acid C-terminal that has been discovered on chromosome 21 within the APP region)

In the updated NIA-AA guideline for AD diagnosis, tau protein evaluation is included in the criteria (18). Flortaucipir the first diagnostic agent moreover, approved by FDA in 2020 to measure tau tangles on a brain PET scan. More conclusive than β-amyloid, CSF elevation of some forms of tau protein, such as total tau (t-tau), phosphorylated tau-181 (p-tau181) and phosphorylated tau-217 (p-tau217), is associated with

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higher risk of AD (65). Although the elevation of t-tau concentration in CSF could also be associated with other disorders such as brain trauma or stroke, which may make it less specific for AD discrimination, it is still considered as one of the three core CSF biomarkers apart from p-tau and β-amyloid (66). The studies have shown about 300% increase in t-tau and 200% increase in p-tau in CSF of AD patients in comparison with the controlled individuals (24).

Although CSF levels of t-tau, p-tau181, and p-tau217 showed acceptable accuracy in detecting AD, their blood levels were not well associated with CSF levels (67). Very recently, several studies with exploiting techniques with higher sensitivity and biomarker enrichment strategies (Table 2), have shown a strong correlation between CSF and plasma levels of both p-tau181 and p-tau217, but not t-tau. These new findings seem promising especially for p-tau217, which performed even better than p-tau181, NfL and MRI in terms of diagnostic accuracy. P-tau217 biomarker not only diagnosed AD individuals, but also was able to discriminate AD from other neurodegenerative disorders. Moreover, it presented predicting capability, as its plasma level was higher in PSEN1 gene mutation carriers without any AD related symptoms, which are expected to develop AD about 20 years later (34, 68-70).

Table 2. AD biomarkers related to Tau protein theory

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ t-Tau in plasma (81 and 96% accuracy)	- BSHRI Site (United States): 16 CU, 16 AD (≥65years) - NTUH Site (Taiwan): 63 CU, 31 AD	Ultra-sensitive Immune-magnetic reduction (IMR) assays	(71)
↑ t-Tau in plasma and CSF (associated with lower CSF Aβ42)	Study 1: 179 AD, 195 MCI, 189 CU Study 2: 561 AD, 212 MCI, 174 cognitive decline, 274 CU	Multiplex xMAP Luminex platform (INNOBIA AlzBio3 kit) & Simoa HD-1 analyzer (Human Total Tau kit)	(67)
↑ t-Tau in plasma (p=0.078)	378 CU - 161 MCI	Quanterix Simoa HD-1 tau assay	(72)
↑ t-Tau in plasma (No correlation between plasma and CSF level)	54 AD - 75 MCI - 25 CU	Digital array technology	(73)
↑ t-Tau in plasma (Weak correlation between plasma and CSF level)	1453 CU (≥65 years, follow-up for a median of 6 years)	Single-molecule array technology	(74)
↑ t-Tau in plasma	71 bvFTD, 83 PPA, 22 controls	Human Total Tau kit with the Simoa HD-1 Analyser	(75)
↔ t-Tau in plasma (No correlation between plasma and CSF level)	111 SCD & 134 CU (age- and gender-matched)	Ultra-sensitive, single-molecule array (Simoa)	(76)
↔ t-Tau in plasma (p=0.227) ↔ p-Tau-181 in plasma (p=0.531)	28 AD – 13 MCI – 6 CU (Taiwanese)	Immunoassays	(49)
↑ p-Tau-181 in Plasma (significant correlation between plasma and CSF level)	Study 1: 20 AD & 15 control Study 2: 20 DS & 22 controls Study 3: 8 AD & 3 other neurological diseases	Ultrasensitive immunoassay	(77)
↑ p-Tau-181 in Plasma ↑ p-Tau-217 in Plasma	Study1 (discovery cohort): 9 Young controls, 8 Aged controls, 2 Non-AD MCI, 5 Preclinical AD, 8 AD-MCI, 2 AD-moderate	Mass spectrometry	(78)

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Table 2. AD biomarkers related to Tau protein theory

Biomarker alteration in body fluid	Studied group	Method	Ref.
	Study2 (validation cohort): 31 Aged controls, 11 Non-AD MCI, 20 Preclinical AD, 24 AD-MCI, 6 AD-moderate		
↑ p-Tau-181 in Plasma (3.5-fold)	Study 1 and 2: 69 CU, 47 MCI, 56 AD_{clin}, 39 CBS, 48 PSP, 50 bvFTD, 27 nfvPPA, 26 svPPA Study 3: 42 participants	Electrochemiluminescence	(69)
↑ p-Tau-181 in Plasma (16 years prior to estimated symptom onset, p= 0.050)	19 symptomatic FAD carriers, 24 pre-symptomatic FAD carriers, 27 non-FAD carriers	In-house single molecule array assay	(79)
↑ p-Tau-217 in Plasma (discriminated AD from other NDD)	Cross-sectional cohorts: Study1: 34 AD, 4 without AD Study2: 301 CU, 178 MCI, 121 AD, 99 other NDD Study3: 365 PSEN1 E280A mutation carriers, 257 mutation noncarriers	Immunoassays	(80)
↑ p-Tau-217 in Plasma	435 CU (followed for about 5 years)	Meso-Scale Discovery platform	(52)
↑ p-tau217 in CSF (6-fold) ↑ p-tau181 in CSF ↑ p-tau231 in CSF	109 CU, 20 MCI, 21 AD, 21 non-AD	Simoa single molecule array	(81)
↑ p-Tau181 in plasma (1.7-fold) ↑ tTau in plasma	Longitudinal study: 85 consisting of individuals with MCI (follow-up for 4 years) Cross-sectional study: 95 AD, 53 other NDD, 90 CU	Electrochemiluminescence immunoassays	(82)
↓ Tau-C in Serum ↓ Tau-A in Serum	5,309 postmenopausal Woman (median 13.7 years follow-up)	Solid phase competitive ELISA	(83)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), NDD (neurodegenerative diseases), FAD (familial Alzheimer's disease), DS (Down syndrome), t-tau (total tau), p-tau181 (phosphorylated tau-181), p-tau217 (phosphorylated tau-217), Tau-C (caspase-3-generated cleavage site at Asp421), Tau-A (The antibodies detect an ADAM10-generated cleavage site at Ala152), bvFTD (behavioral variant frontotemporal dementia), PPA (primary progressive aphasia), SCD (subjective cognitive decline), AD_{clin} (clinically distinguished AD), PSP (progressive supranuclear palsy), CBS (corticobasal syndrome), bvFTD (behavioral variant frontotemporal dementia), nfvPPA (nonfluent variant primary progressive aphasia), svPPA (semantic variant PPA individuals).

Neurofilament Light (NfL)

Neurofilament light (NfL) protein is a structural protein found primarily in large-caliber myelinated axons in the brain. Following neuro-axonal damage, NfL releases to the environment and can be tracked in CSF. Neuronal loss is a normal part of aging and causes an annual increase in NfL baseline. However, longitudinal studies have shown that high NfL levels in the CSF are indicative of brain atrophy and a recognized biomarker for neurodegeneration (84, 85). Although CSF and serum NfL levels are demonstrated to be highly correlated, the very low concentration of peripheral NfL makes it undetectable by conventional methods. New advances in sensitive detection technologies enable scientists to detect low concentrations of NfL in peripheral blood hence studies are no longer limited to CSF. However, NfL is not a specific biomarker.

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In a two multicenter cohorts with more than 2250 cases, done by Ashton and coworkers, plasma NfL was shown to be significantly increased in all cortical neurodegenerative disorders, amyotrophic lateral sclerosis, atypical parkinsonian disorders, and Down syndrome-associated dementia (84). NfL seems to be a promising biomarker of neurodegenerative disease progression, and can be used for monitoring treatment efficacy and assessment of clinical trials (86). Enzymes and other protein-based biomarkers that have been investigated for possible biomarker of AD are summarized in Table 3.

Table 3. Enzymes and other protein-based biomarkers for AD.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ NfL in Serum (association between serum NfL and brain volume changes in >60 y)	Population-based cohort study with a 5.9-year follow-up (n = 103)	Single molecule array (Simoa)	(85)
↑ NfL in Serum (p< 0.001, correlated with CSF biomarkers: low Aβ42 [p=0.001], high T-tau [p=0.02], high p-tau [p=0.02])	401 CU, 855 MCI, 327 AD	Ultrasensitive ELISA	(87)
↑ NfL in Serum (predict early pre-symptomatic familial AD)	187 CSF & 405 serum of individuals with 50% risk of carrying an autosomal-dominant AD mutation in one of three genes: APP, PSEN1, PSEN2	Ultrasensitive immunoassay	(86)
↑ NfL in Plasma	435 CU (followed for about 5 years)	Simoa-based assay	(52)
↑ NfL in plasma	Longitudinal study: 85 consisting of individuals with MCI (follow-up for 4 years) Cross-sectional study: 95 AD, 53 other NDD, 90 CU	Electrochemiluminescence immunoassays	(82)
↑ PTP in serum (1.54-fold, p<0.0001) ↑ Superoxide dismutase in plasma (1.16-fold, p<0.0001)	AIBL cohort: 754 controls & 207 AD ADNI cohort: 58 controls & 112 AD	151-analyte multiplex panel & sandwich ELISA & mass spectroscopy	(88)
↑ PTP in serum (1.33-fold) ↑ von Willebrand factor in serum (1.29-fold) ↓ Prostatic acid phosphatase in serum (0.78-fold)	197 AD and 203 controls [187 & 190 were white, respectively]	Multiplex fluorescent immunoassay	(89, 90)
↑ Superoxide dismutase in plasma (1.16-fold, p< 0.0001) ↓ Albumin in plasma (0.95-fold, p< 0.0001)	207 AD & 754 controls	Multiplex panel (Human DiscoveryMAP)	(88)
↑ Keratin type 2 in plasma (~ 2.5-fold (p < 0.001)) ↓ Albumin in plasma (> 2-fold (p < 0.01))	12 MCI & 12 control	Western blotting	(91)
↑ Albumin in plasma (1.1-fold (p<0.05))	25 AD (11 males, 14 females), 25 hospitalized patients as control (10 males, 15 females)	Immunonephelometric method	(92)
↓ Serum albumin precursor in plasma (0.09-fold, p=0.0250) ↑ Desmoplakin in plasma (1.78-fold, p=0.0003)	50 AD & 50 controls	Mass Spectrometry	(93)

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Table 3. Enzymes and other protein-based biomarkers for AD.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↓ ADNP in serum (5-fold, $p < 0.05$) ↑ Actin in serum ↑ ITIH4 in serum ↑ ATIII in serum ($p < 0.05$)	45 early-stage AD (ages: 63–84 years with a mean of 77.2) & 20 control (ages: 55–84 years with a mean of 72.3)	Western blotting & ELISA & 2D gel electrophoresis combined with nano-HPLC-ESI-MS/MS	(94)
↓ REST in plasma	AddNeuroMed cohort: 65 healthy elderly, 36 stable MCI, 29 converter MCI, 65 AD	Sandwich enzyme-linked immunosorbent assay	(95)
↑ Hyperphosphorylated TDP-43 in plasma (in 46% of FTD vs. 22% of AD vs. 8% of control)	35 with FTD, 102 AD, 85 control subjects	ELISA	(96)
↑ Cystatin C in plasma ($p < 0.001$)	88 patients with dementia (43 AD, 45 VAD) & 45 controls	Latex-enhanced reagent, Behring BN ProSpec Analyzer	(97)
↓ AGT in plasma ↑ IGFBP-2 in plasma ↑ OPN in plasma ↓ SAP in plasma ↑ Cathepsin D in plasma	98 AD & 101 elderly controls	Luminex xMAP technology	(98)
Multiple CSF protein biomarker panels Synaptic and metabolic: ↑in CSF - ↓in brain Glial-enriched myelination and immunity: ↑in CSF - ↑in brain	Multiple studies	Mass spectrometry & Multiplex tandem mass tag (TMT)	(99)

NfL (Neurofilament light), PTP (pancreatic thread protein), ADNP (activity-dependent neuroprotector homeobox protein), ITIH4 (Inter-alpha-trypsin inhibitor heavy chain H4), ATIII (Anti-thrombin-III), REST (Repressor element 1-silencing transcription), FTD (frontotemporal dementia), AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), VAD (Vascular dementia), TDP-43 (TAR DNA binding protein 43)

Inflammation and immune based biomarkers

In addition to β-amyloid and tau pathologies, some other pathological pathways at the molecular level have also been reported in the literature. As one of the key pathways, inflammation and inflammatory processes have attracted much attention in AD development and progression. Inflammation was assumed a subsequent of Aβ deposition; nonetheless, clinical studies have shown that inflammatory responses are evident much earlier, in preclinical AD independently of Aβ deposition. In fact, AD is also characterized by neuroinflammation, and it is believed that immune system contributes, at least in some part, to the pathogenesis and exacerbation of AD. For instance, brain's microglia drives the neuroinflammation which exacerbates with disease progression (100, 101).

Although still controversial, several investigations' results claimed that use of nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of AD (102). The results were also supported by a recent meta-analysis undertaken by Zhang et al. (103). However, the efficacy of NSAIDs still needs further investigation. Genomics studies also have revealed the role of immune system in predisposing to AD (104).

According to our comprehensive literature survey, more than hundred inflammatory cytokines, in total, have been reported to change in blood levels of individuals with AD (Table 4). Some of these biomarkers

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are anti-inflammatory (e.g., TGF-β, IFN-γ, and IL-10) while most of them are pro-inflammatory cytokines (e.g., TNF-α, IL-2, IL-4, IL-6, CRP, complement factors, and β2-microglobulin).

Aside from whether the inflammatory responses are "deleterious or beneficial" in AD pathology, the analytes can provide valuable insights into the state of the disease. Pillai et al. used a multiplex system for investigation of inflammatory pathways in AD and showed that inflammation-based biomarkers correlate well with neurodegeneration state and cognition decline. TNF signaling pathway, complement and coagulation cascade correlated with tau and $A\beta_{42}$ levels, respectively. The post-mortem brain tissue transcriptomics also revealed the overexpression of correlated genes (105). Morgan and co-workers, reported ten plasma biomarkers (including factor H, factor B, C3, C4, C5, MCP-1, CRP, sCR1, Eotaxin-1, and MIP-1b) involved in inflammatory pathways which can discriminate AD from non-AD individuals. sCR1, MCP-1, and Eotaxin-1 could even optimally differentiate AD and MCI patients (106).

In most studies plasma level of Creactive protein (CRP) was used for differentiating AD from control group since it decreases as AD progresses (106, 107). Increased plasma level of glial fibrillary acidic protein (GFAP) was also detected in MCI patients developing AD during the follow up studies (82, 108).

According to subtypes and stages of AD, contribution of inflammatory and immune-related biomarkers may be different, accompanying various hallmarks and risk factors (109). Nevertheless, multiplex detection of inflammatory biomarkers might be a doorway towards early diagnosis of AD. Table 4 shows the Inflammatory and immune based AD biomarkers.

Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
TNF-related biomarkers			
TNF-α			
↑ in peripheral blood (p= 0.01)	680 AD & 447 controls (Pooled from 14 studies)	A Meta-Analysis of Cytokines in AD	(110)
↑ in serum (~ 1.65-fold in severe AD, p<0.001)	11 severe AD & 25 mild AD	ELISA	(111)
↓ in plasma (2.6-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
↓ in Serum (0.74-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)
↔ in Serum	34 AD, 33 VAD, 30 control	ELISA	(113)
↔ in Plasma (p=0.41))	28 AD, 13 MCI, 60 control (Taiwanese)	Immunoassays	(49)
TNF- β			
↑ in Serum (1.37-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)
↓ in Serum (0.65-fold)	32 AD & 19 Controls	ELISA	(114)
TRAIL-R4			
↑ in plasma (1.8-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
TNF receptor like 2			

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Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ in Plasma (1.27-fold, p= 0.0002)	207 AD & 754 controls	Multiplex panel (Human DiscoveryMAP)	(88)
sTNFR-II			
↓ in Serum (0.7-fold)	32 AD & 19 Controls	ELISA	(114)
TGF-β			
↑ in peripheral blood (p=0.0006)	190 AD & 158 controls (Pooled from 5 studies)	A Meta-Analysis of Cytokines in AD	(110)
↓ in Serum (0.77-fold)	32 AD & 19 Controls	ELISA	(114)
↔ in Serum	30 Probable AD & 25 control	Radioimmunoassay	(115)
Interferons			
IFN-α			
↔ in Plasma	20 AD & 17 controls	ELISA	(116)
IFN-γ			
↔ in peripheral blood (p=0.55)	113 AD & 102 controls (Pooled from 4 studies)	A Meta-Analysis of Cytokines in AD	(110)
↔ in Serum	30 Probable AD & 25 control	Radioimmunoassay	(115)
↔ Plasma	20 AD & 17 controls	ELISA	(116)
Interleukins			
IL-1β			
↑ in peripheral blood (p=0.00001)	574 AD & 370 controls (Pooled from 10 studies)	A Meta-Analysis of Cytokines in AD	(110)
↑ in plasma (~ 10-fold, p<0.001- Detectable in 17 cases of AD but only in 1 control)	145 AD & 51 control	ELISA	(117)
↔ in Plasma	11 Sporadic AD, 22 PD, 12 control	ELISA	(118)
↔ in Serum	34 AD, 33 VAD, 30 control	ELISA	(113)
↔ in serum (p=0.95)	11 severe AD & 25 mild AD	ELISA	(111)
↔ in Serum	40 AD, 20 PD, 42 control	ELISA	(119)
IL-1α			
↓ in plasma (2.9-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
IL-1rα			
↓ in Serum (0.81-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)
IL-2			
↔ in Plasma	11 Sporadic AD, 22 PD, 12 control	ELISA	(118)
IL-3			
↓ IL-3 in plasma (2.0-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
IL-4			
↔ in peripheral blood (p=0.59)	68 AD & 66 controls (Pooled from 4 studies)	A Meta-Analysis of Cytokines in AD	(110)
IL-6			

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Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ in peripheral blood (p=0.00001)	985 AD & 680 controls (Pooled from 14 studies)	A Meta-Analysis of Cytokines in AD	(110)
↑ in Plasma (5-fold)	128 AD & 83 controls (Japanese)	ELISA	(120)
↑ in Plasma (6-fold - Detected in 53% of AD and 27% of controls)	145 AD & 51 control	ELISA	(117)
↑ in Plasma (~5.5-fold, p=0.032)	20 AD & 17 controls	ELISA	(116)
↑ in Serum (~ 6.4-fold in severe AD, no change in mild-moderate AD)	26 Severe AD, 15 mild-moderate AD & 24 control	ELISA	(121)
↑ in Serum	34 AD, 33 VAD, 30 control	ELISA	(113)
↔ in Plasma (p=0.65)	28 AD, 13 MCI, 60 control (Taiwanese)	Immunoassays	(49)
↔ in Plasma	11 Sporadic AD, 22 PD, 12 control	ELISA	(118)
↔ in Serum	41 AD & 32 control	ELISA	(122)
↔ IL-6 in Serum	97 AD & 79 control (age- and sex-matched)	Bioassay	(123)
sIL-6R			
↓ in Serum (~0.84-fold, p<0.001)	41 AD & 32 control	ELISA	(122)
IL-8 (CXCL8)			
↑ in plasma (1.7-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
↑ in Serum (1.15-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)
↔ in peripheral blood (p=0.36)	69 AD & 64 controls (Pooled from 3 studies)	A Meta-Analysis of Cytokines in AD	(110)
IL-10			
↑ in Plasma (1.10-fold, p< 0.0001)	207 AD & 754 controls	Multiplex panel (Human DiscoveryMAP)	(88)
↓ in Serum (0.76-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)
↔ in Serum	30 Probable AD & 25 control	Radioimmunoassay	(115)
↔ in peripheral blood (p=0.90)	156 AD & 123 controls (Pooled from 4 studies)	A Meta-Analysis of Cytokines in AD	(110)
IL-11			
↑ in plasma (2.1-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
IL-12			
↑ in peripheral blood (p < 0.00001)	148 AD & 106 controls (Pooled from 5 studies)	A Meta-Analysis of Cytokines in AD	(110)
↔ in Plasma	20 AD & 16 controls	ELISA	(116)
↔ in Serum	30 Probable AD & 25 control	Radioimmunoassay	(115)
IL-15			
↑ in Serum (1.26-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)
IL-17			

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Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↓ in Plasma (0.87-fold, p< 0.0001)	207 AD & 754 controls	Multiplex panel (Human DiscoveryMAP)	(88)
IL-18			
↑ in peripheral blood (p=0.03)	131 AD & 94 controls (Pooled from 4 studies)	A Meta-Analysis of Cytokines in AD	(110)
Other biomarkers			
↔ CRP in peripheral blood (p=0.67)	253 AD & 155 controls (Pooled from 5 studies)	A Meta-Analysis of Cytokines in AD	(110)
↓ CRP in plasma ↓ CRP in serum	Plasma test: 112 AD & 52 control Serum test: 197 AD & 199 control	Multiplex fluorescent	(107)
↓ CRP in Plasma (Differentiate AD from control) ↑ Complement C4 in Plasma (Differentiate AD from control) ↑ Complement C3 in Plasma (Differentiate AD from control) ↑ Complement C5 in Plasma (Differentiate MCI from control) ↑ CCL2 in Plasma (Differentiate AD from control) ↑ Factor H in Plasma (Differentiate MCI from control) ↓ Factor B in Plasma (Differentiate MCI from control) ↓ sCR1 in Plasma (Differentiate AD from control)	262 AD, 199 MCI, 259 control	Commercial and In-house Singleplex and Multiplex assays	(106)
↔ CRP in Plasma ↑ ACT in Plasma (~ 1.25-fold, p<0.001) ↔ Neopterin in Plasma	145 AD & 51 control	Radial immune-diffusion kit & ELISA	(117)
↓ CRP in Serum (0.86-fold) ↑ NTP in Serum (1.33-fold) ↑ α2M (α-2-macroglobulin) in Serum (2.45-fold) ↑ B-2-microglobulin in Serum (1.36-fold) ↓ CCL3 in Serum (0.70-fold) ↓ Creatine kinase MB in Serum (0.80-fold) ↓ G-CSF in serum (0.7-fold) ↑ IGFBP-2 in Serum (1.23-fold) ↑ TPO in Serum (2.18-fold) ↑ Eotaxin 3 in Serum (1.26-fold) ↑ Tenascin C in Serum (1.60-fold) ↑ Fas ligand in Serum (1.03-fold) ↑ Prolactin in Serum (1.21-fold) ↑ Resistin in Serum (1.17-fold)	197 AD & 203 controls	Multiplex fluorescent immunoassay	(89, 90)

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Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↓ SCF in Serum (0.74-fold) ↓ S-100B in Serum (0.72-fold) ↓ Prostatic acid phosphatase in Serum (0.78-fold)			
↔ CRP in Serum ↔ SAP in Serum	140 AD & 30 control	ELISA	(124)
↓ Complement C4 precursor in Plasma (0.49-fold, p=0.0206) ↓ CD5 antigen-like precursor in Plasma (0.62-fold, p=0.0290) ↑ α2M precursor in Plasma (8.83-fold, p=0.0060) ↑ CFH precursor in Plasma (13.7-fold, p=0.0014) ↑ Ig kappa chain C region in Plasma (2.11-fold, p=0.0013) ↑ Ig lambda chain C regions in plasma (2.43-fold, p=0.0054) ↓ ITIH4 precursor in Plasma (0.24-fold, p=0.0155)	50 AD & 50 controls	Mass Spectrometry	(93)
↑ Complement C4 in plasma ↑ β-2-microglobulin in Plasma ↑ BDNF in plasma	98 AD & 101 CU controls	Luminex xMAP technology	(98)
↑ CD40 in Plasma (1.21-fold, p=0.040) ↑ AAT in Plasma (1.11-fold, p=0.0003) ↑ NTP in Plasma (1.54-fold, p<0.0001) ↑ β-2-microglobulin in Plasma (1.24-fold, p=0.006) ↑ CCL3 in Plasma (1.12-fold, p=0.006) ↑ B lymphocyte chemoattractant in Plasma (1.45-fold, p=0.002) ↑ Carcinoembryonic antigen in Plasma (1.4-fold, p=0.001) ↑ MMP-2 in Plasma (1.13-fold, p=0.001) ↑ MMP-9 in Plasma (1.19-fold, p=0.001) ↑ TIMP-1 in Plasma (1.18-fold, p=0.0003) ↑ VCAM-1 in Plasma (1.18-fold, p<0.0001) ↓ EGFR in Plasma (0.89-fold, p=0.012) ↑ IGFBP-2 in Plasma (1.61-fold, p<0.0001) ↑ Angiopoietin 2 in Plasma (1.23-fold, p=0.003) ↑ Homocysteine in plasma (1.23-fold, p=0.002)	207 AD & 754 controls	Multiplex panel (Human DiscoveryMAP)	(88)

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Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ Erythrocyte sedimentation rate in plasma (1.46-fold, p=0.002) ↑ Cortisol in Plasma (1.28-fold, p<0.0001)			
↑ Lcn2 in plasma	38 Controls, 41 MCI, 62 AD	ELISA	(125)
↓ Lcn2 in CSF ↔ Lcn2 in serum	26 AD, 28 MCI, 26 Control	ELISA	(126)
↔ ACT in Serum	40 AD, 20 PD, 42 control	ELISA	(119)
↑ AAT in serum (~2-fold) ↑ ITIH4 in Serum	45 early-stage AD, 20 control	ELISA & 2D gel electrophoresis combined with nano-HPLC-ESI-MS/MS & western blotting	(94)
↑ NTP in Serum (40-fold than CSF, correlation between serum and CSF and between the CSF/serum albumin ratio (BBB damage marker))	-	Microparticle enzyme immunoassay	(127)
↑ CCL2 in CSF (p < 0.005)	21 AD		(128)
↑ CCL5 in Plasma ↑ CCL15 in Plasma ↑ CCL18 in Plasma ↑ EGF in Plasma ↑ GDNF in Plasma (~22-fold)	96 AD, 44 MCI, 42 depression with or without cognitive impairment, 19 controls	Searchlight Multiplex ELISA	(129)
↑ GFAP in plasma ↔TREM2 in plasma	-	Simoa technology & MS.	(108)
↑ GFAP in plasma (1.6- fold)	Longitudinal study: 85 consisting of individuals with MCI (follow-up for 4 years) Cross-sectional study: 95 AD, 53 other NDD, 90 CU	Electrochemiluminescence immunoassays	(82)
↓ CCL5 in Plasma (2.9-fold) ↓ CCL7 in Plasma (1.7-fold) ↓ CCL15 in Plasma (1.6-fold) ↑ CCL18 in Plasma (1.9-fold) ↑ ICAM-1 in Plasma (2.2-fold) ↓ EGF in Plasma (2.7-fold) ↓ G-CSF in Plasma (1.9-fold) ↓ M-CSF in Plasma (2.4-fold) ↓ PDGF-BB in Plasma (3.4-fold) ↓ GDNF in Plasma (1.8-fold) ↑ IGFBP-6 in Plasma (1.5-fold) ↑ Angiopoietin 2 in Plasma (2.1-fold)	85 AD, 47 MCI, 11 other dementias, 21 other neurological diseases, 79 control	Filter-based, arrayed sandwich ELISA (microarray)	(112)
↓ CCL5 in Plasma ↓ BDNF in Plasma ↓ Leptin in Plasma	95 AD & 88 Controls	Sandwich ELISA	(114)
↓ MSP-α in Serum (0.76-fold) ↓ NAP-2 in Serum (0.67-fold) ↓ NT-3 in Serum (0.7-fold)	32 AD & 19 Controls	ELISA	(114)

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Table 5. Inflammatory and immune based AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↓ TIMP-1 in Serum (0.72-fold) ↓ TIMP-2 in Serum (0.75-fold) ↓ FGF in Serum (Basic FGF: 0.67-fold - FGF-6: 0.66-fold) ↓ TPO in Serum (0.71-fold)			
↓ FGF21 in plasma ↔ GDF15 in plasma (↑ DM2) ↓ Humanin (HN) in plasma	102 centenarian offspring (OFF), 92 controls, 162 DM2 without complications, 93 DM2 with complications, 120 AD	ELISA	(130)
↑ CCL15 (1.2-fold) ↔ CCL18 in Plasma ↔ ICAM-1 in Plasma ↑ EGF in Plasma (1.3-fold) ↑ PDGF-BB in Plasma (1.3-fold) ↔ Angiotensin in Plasma	142 AD, 174 control, 88 other dementias	Antibody array	(131)
↓ IgG anti-Aβ42 in Serum (0.4-fold, $p<0.01$)	39 AD & 39 controls	ELISA	(59)
↔ Isoprostanes in Plasma	12 AD, 25 probable AD, 5 dementia with Lewy bodies and HD as a control group		(132)
↑ ACE in CSF ↑ Angiotensinogen in CSF ↑ Angiotensin in CSF	20-21 AD, 8-10 MCI, 25-28 control	ELISA	(133)
↑ Homocysteine in Plasma (>14 μmol/L almost doubled the risk of AD)	1092 CU among whom 83 developed to AD over a median follow-up period of 8 years	HPLC	(134)
↓ Eotaxin-1 in Plasma (Differentiate AD from control)	262 AD, 199 MCI, 259 control	Commercial and In-house Singleplex and Multiplex assays	(106)

AD (Alzheimer's disease), CU (cognitively unimpaired), MIC (mild cognitive impairment), VAD (Vascular dementia), PD (Parkinson's disease), HD (Huntington's disease), AAT (α-1-antitrypsin), ACE (angiotensin-converting enzyme), ACT (α-1-antichymotrypsin), BDNF (brain-derived neurotrophic factor), BNT77 (IgA anti- Aβ 11-28), CCL15 (MIP-1-δ, Leukotactin-1, MIP-5, HCC-2, NCC-3), CCL18 (MIP4, PARK, PARC), CCL2 (MCP-1: monocyte chemoattractant protein-1), CCL3 (MIP1α macrophage inflammatory protein 1-α), CCL5 (RANTES), CCL7 (MCP-3), CRP (Creactive protein), FGF (Fibroblast growth factor), GDNF (glial-derived neurotrophic factor), GFAP (glial fibrillary acidic protein), ICAM-1 (intercellular adhesion molecule-1), IGFBP (Insulin like growth factor binding protein), ITIH4 (Inter-alpha-trypsin inhibitor heavy chain H4), Lcn2 (Lipocalin), MMP (Matrix metalloproteinase), MSP-α (Macrophage stimulating protein-α), NAP-2 (Neutrophil activating peptide-2), NT-3 (Neurotrophin-3), NTP (neuronal thread protein or pancreatic thread protein), PDGF-BB (platelet-derived growth factor BB), S-100B (pro-inflammatory agent), SAP (glycoprotein serum amyloid P), SCF (Stem cell factor), sCR1 (Plasma soluble complement receptor 1), sIL-6R (Soluble IL-6 receptor), sTNFR-II (soluble TNF receptor II), sTREM2 (soluble triggering receptor expressed on myeloid cells 2), TIMP (Tissue inhibitor of metalloproteinase), TRAIL-R4 (TNF-related apoptosis-inducing ligand receptor-4), TPO (Thrombopoietin), VCAM-1 (vascular cell adhesion molecule 1), GDF (Growth Differentiation Factor 15), DM2 (type 2 diabetes mellitus)

Genetic materials

The role of genetic factors in predisposition to AD is evident now. About 25% of AD is familial (135) and the heritability of the disease is estimated to be up to 80% (136). Since the discovery of three mutations (in Amyloid precursor protein, Presenilin 1, and Presenilin 2) causing autosomal dominant AD (with a prevalence of <1%), the search for other genetic risk loci for the more common form of AD (the late-onset) was massively started. To date, more than 25 established risk genes involved in AD susceptibility have been

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discovered (136-138). Genome-Wide Association Studies (GWAS) and the International Genomics of Alzheimer's Project (IGAP) consortium have had a considerable role in advancing polygenic basis of AD. Although "neither necessary nor sufficient for the disease" (135), ε4 allele of ApoE has the most genetic risk for both early- and late-onset AD (139). Recently, the ApoE status and polygenic risk scores (PRS) have attracted much attention as genetic biomarkers for AD prediction (140).

Genetic alterations may also be revealed through transcriptomics, i.e., at RNA level. Indeed, genetic variants are not always affecting the pathophysiology directly. Sometimes the alteration is at the gene regulation and/or post translational modifications (PTM) levels (136). Gene dysregulations that contribute to AD occur early in the course of the disease pathology process. Transcriptomics can be applied to identify ill gene expressions in (preclinical stage of) AD (141) and therefore is useful for diagnosis/prediction of the disease through body fluids. We summarized investigated transcriptome in Table 5.

Table 6. AD biomarkers related to genetic materials

Biomarker alteration in body fluid	Studied group	Method	Ref.
7-miRNA signature in plasma (95% accuracy): ↓ hsa-let-7d-5p ↓ hsa-let-7g-5p ↓ hsa-miR-15b-5p ↓ hsa-miR-142-3p ↓ hsa-miR-191-5p ↓ hsa-miR-301a-3p ↓ hsa-miR-545-3p	Cohort 1: 11 AD, 9 MCI and 20 CU Cohort 2: 20 AD, 17 CU	TaqMan qPCR	(142)
12-miRNA signature in plasma (93% accuracy): ↓ hsa-let-7f-5p ↓ hsa-miR-1285-5p ↓ hsa-miR-107 ↓ hsa-miR-103a-3p ↓ hsa-miR-26b-Sp ↓ hsa-miR-26a-Sp ↓ hsa-miR-532-Sp ↑ hsa-miR-151a-3p ↑ brain-mir-161 ↑ hsa-let-7d-3p ↑ brain-miR-112 ↑ hsa-miR-5010-3p	Study1: 48 AD & 22 control Study2: 94 AD & 18 control	RT-qPCR	(143)
16-miRNA signatures with ApoE ε4 in plasma: ↓ hsa-miR-1306-5p ↓ hsa-miR-342-3p ↓ hsa-miR-15b-3p ↑ hsa-miR-361-5p ↑ hsa-miR-30e-5p ↑ hsa-miR-93-5p ↑ hsa-miR-15a-5p	16 AD & 36 control	qRT-PCR	(144)

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Table 6. AD biomarkers related to genetic materials

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ hsa-miR-143-3p ↑ hsa-miR-335-5p ↑ hsa-miR-106b-5p ↑ hsa-miR-101-3p ↑ hsa-miR-424-5p ↑ hsa-miR-106a-5p ↑ hsa-miR-18b-5p ↑ hsa-miR-3065-5p ↑ hsa-miR-20a-5p ↑ hsa-miR-582-5p			
↑ miRNA-34a in plasma and PBMCs ↑ miRNA-34c in plasma and PBMCs	78 AD & 85 control 25 AD &. 27 control	TAQMAN MicroRNA REAL TIME qPCR	(145)
↓ miR-146b-5p in Peripheral blood ↓ miR-15b-5p in Peripheral blood	40 AD & 31 CU	PAXgene Blood miRNA Kit (Qiagen, Germany)	(146)
↑ miR-92a-3p in plasma (p=0.0442) ↑ miR-181c-5p in plasma (p=0.0024) ↑ miR-210-3p in plasma (p=0.0006)	38 CU, 26 MCI, 56 AD, 27 FTD	RT-qPCR	(147)
↓ miR-9 in whole blood (3-fold, p=0.001)	36 probable AD & 38 controls (women)	RT-qPCR	(148)
↓ Heme oxygenase-1 (HO-1) mRNA in plasma	46 AD & 25 controls, 13 PD, 30 MCI, 9 control	Northern blotting	(149)
RNA signature in whole-blood (170 oligonucleotide probe sets associated with 133 genes)	80 AD & 70 control	RT-PCRs	(150)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), FTD (frontotemporal dementia)

Metabolic biomarkers

The idea that AD is basically a metabolic disorder in which different biochemical metabolic pathways run in a pathologic way is growing (151). Having immediate correlation with cell functions, metabolic pathways are considered as the "last avenue to explore" and the most straightforward indicative of pathophysiological conditions (152).

Metabolomics of AD vs. non-AD subjects revealed multiple metabolic pathways are affected. Lipid biosynthesis and metabolism (153-156), cholesterol, sphingolipids, and glycerophospholipids metabolism and transport (155, 157), neurotransmitter metabolism and signaling (151, 155, 158), amino acid metabolism (151, 155, 158), transmethylation (151), polyamine synthesis and catabolism (151), glucose metabolism (159), energy metabolism (155, 160, 161), Krebs cycle (155), urea cycle (151), mitochondrial function (151, 155), aminoacyl-tRNA biosynthesis (155), glutathione synthesis and oxidative stress (151, 160), and hyperammonemia (160) are examples of affected metabolic pathways in AD patients vs. controls. It seems that abnormality in basic metabolic pathways such as glycolysis and transmethylation may upset other related metabolic pathways (151).

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It has been shown that the metabolic abnormalities may start at pre-clinical stage (159) and that the severity and the progression of the disease is associated with the metabolite concentrations (151, 157). Sphingolipids (157), desmosterol and desmosterol/cholesterol ratio (162) have been suggested as specific biomarkers for early diagnosis of AD (Table 6).

In a metabolomics screening of 73 CSF samples, diagnostic accuracy based on the proposed biomarkers was 83%, which is claimed to be more accurate compared with using classical biomarkers ($A\beta_{42}$ and tau) (158).

Table 7. Metabolic AD biomarkers

Biomarker alteration in body fluid	Studied group	Method	Ref.
Lipids			
↓ ApoE in plasma (0.97-fold, p= 0.042)	207 AD & 754 controls	ELISA (commercial assay)	(88)
↓ ApoE in plasma ↑ ApoCIII in serum ↑ Lipoprotein (a) in serum	203 off-springs of AD & 197 non-AD parents (Texas Alzheimer's Research Consortium)	Multiplex fluorescent immunoassay	(89, 90)
↓ ApoA1 in serum (0.8-fold, $p=10^{-7}$) ↓ HDL in serum (0.7-fold, $p=10^{-7}$)	98 AD & 59 controls	Immunonephelometry on Behring Nephelometer Analyzer, with Behring reagents	(165)
↑ ApoA-IV in serum ($p<0.05$)	45 early-stage AD & 20 control	ELISA & 2D gel electrophoresis combined with nano-HPLC-ESI-MS/MS	(94)
↑ Cholesterol in serum	411 AD or normal, 87 having both the ApoE genotype and TC	-	(166)
↓ Cholesterol in serum (0.92-fold, $p<0.05$) ↔ TG (triglycerides) in serum (0.7-fold, $p<0.0000001$)	80 AD & 59 controls	Enzymatic methods	(165)
↔ Cholesterol in plasma ($p<0.31$) ↑ 24S-Hydroxycholesterol in plasma (1.25-fold, $p<0.001$)	30 AD & 30 controls	Enzymatic methods & Isotope dilution–mass spectrometry	(167)
↔ Cholesterol in plasma ($p>0.05$) ↓ 24S-Hydroxycholesterol in plasma ($p<0.05$) ↓27-Hydroxycholesterol (0.78-fold, $p<0.01$) ↔ HDL in plasma ($p>0.05$)	20 AD, 8 MCI, 25 controls	Isotope dilution–mass spectrometry	(133)
↓ HDL in plasma	43 AD, 45 VAD, 45 controls	Enzymatic methods (commercial kits)	(97)
↓ HDL in plasma	103 women (age 97.7 ± 0.2) & 37 men (age 97.6 ± 0.4)	-	(168)
↑ Cortisol in plasma (1.28-fold, $p<0.0001$)	AIBL cohort: 754 controls & 207 AD ADNI cohort: 58 controls & 112 AD	ICP-MS & 151-analyte multiplex panel & sandwich ELISA	(88)

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Table 7. Metabolic AD biomarkers

Biomarker alteration in body fluid	Studied group	Method	Ref.
↓ Progranulin in plasma	70 control, 72 early-onset probable AD, 9 symptomatic and 18 asymptomatic relatives of *GRN* mutation families	ELISA	(169)
↑ Clusterin (Apo J) in plasma	Discovery cohort: 95 Validation cohort: 689 (additional 60 subjects)	Sandwich ELISA & Two-dimensional gel electrophoresis and LC-MS-MS	(170)
↑ Clusterin (Apo J) in plasma ($p<0.15$)	16 MCI among 139 non-demented (with longitudinal monitoring)	ELISA	(171)
↑ Clusterin (Apo J) in plasma	98 AD & 101 controls	Luminex xMAP technology	(98)
↔ Clusterin (Apo J) in plasma	171 control, 127 AD, 82 with other dementias, 30 with depression	ELISA	(172)
Others			
↑2,4-dihydroxybutanoic acid in serum ($p=0.0048$)	46 controls, 143 MCI, 47 AD	GC–TOFMS & UPLC/MS	(173)
↑ Glutamine in plasma ↓ Piperine in plasma	Study1: 43 AD, 45 MCI, 41 controls Study2: 50 AD, 18 controls	LC–MS	(174)
↓ 3 acylcarnitines: Decanoylcarnitine Pimelylcarnitine Tetra decadienylcarnitine	longitudinal clinical-pathologic cohort studies of aging and dementia: 436 Non-Converter & 85 Converter	Biocrates AbsoluteIDQ® p180 Kit & FIA-MS/MS & UPLC-MS/MS	(175)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), VAD (Vascular Alzheimer's disease), TC (Total serum cholestrerol)

ApoE genotype may affect metabolic pathways (163). A metabolomics analysis revealed that ApoE4 genotype might changes lipid metabolism and increases lysophosphatidylcholine and glycerophospholipids in early stages of AD. Based on these metabolites the authors reported the satisfactory discrimination of early AD patients from healthy controls with $R^2=0.738$ (164).

Vitamins and bio-metals

The role of vitamins contributing to AD was investigated by several studies. Vitamin D, E, A, C, B_{12}, and folate are the most prominent ones. Hyperhomocysteinemia is also shown to be prevalent in AD patients (Table 7).

Nevertheless, the effect size of these elements is not that significant, and the findings are controversial. While some researchers say that concurrent use of vit. C and E are associated with a reduced risk of AD (176), there are studies which showed that neither intake of antioxidant vitamins such as carotenes, vit. C, and vit. E has any effect on lowering the risk of AD development (177) nor high doses of vit. B and folate has any effect on slowing cognitive decline (178). Vit. D is another vitamin that its contribution in AD is controversial. A meta-analysis showed that the risk of AD development is not associated with the level of vit. D (179). More details can be found in Table 7.

The investigations have revealed the dyshomeostasis of metal ions in AD. Findings show modified expression levels and distribution of bio-metal transporters in AD, as well as accumulation of transition

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metals such as zinc, iron, and copper, in the brain of patients (180, 181). Although the exact pathological role of the transition metals has not been determined, some studies suggest the accumulation of these metals may be associated to AD (182) via acceleration of Aβ deposition (183) and microtubule anomaly induction (184). The co-measurement of plasma metals has been suggested as potential BBBs for AD diagnosis as shown in table 7 (185-187).

Table 8. Vitamin and bio-metal AD biomarkers

Biomarker alteration in body fluid	Studied group	Method	Ref.
Vitamins			
↓ Vitamin B12 in serum (p<0.001)	108 Control, 164 Clinically diagnosed AD, 76 Histologically confirmed AD	Radioimmunoassay	(188)
↓ Vitamin C in plasma (AD (p<0.001), VAD (p<0.001), PD & dementia (p<0.01)) ↓ Vitamin A in plasma (AD (p<0.01), VAD (p<0.001)) ↓ Vitamin E in plasma (AD (p<0.01), VAD (p<0.001))	79 AD, 37 VAD, 18 PD & dementia, 58 Matching control & 41 PD, 41 Matching controls	Fluorimetric assay & HPLC	(189)
↓25-hydroxy vitamin D in plasma	10186 (white Danish general population- During 30 years of follow-up, 418 developed AD and 92 developed VAD)	DiaSor in Liaison 25(OH)D TOTAL assay	(190)
Biometals			
↑ Zinc in serum (1.9-fold)	9 AD & 8 controls	Flame atomic absorption spectrometry	(191)
↓ Zinc in plasma (0.91-fold, P< 0.0001)	207 AD & 754 controls	ICP-MS	(88)
↓ Zinc in serum (p=0.043) ↔ Copper in serum (p=0.560)	28 AD, 13 MCI, 6 control (Taiwanese)	Flame atomic absorption spectrometry	(49)
↓ Zinc in serum (0.89-fold, p = 0.0007) ↑ Arsenic in serum (p <0.0001) ↑ Aluminum in serum (1.6-fold) ↑ Chromium in serum (1.3-fold) ↓ Iron in serum (0.74-fold)	44 AD & 41 control	ICP-MS	(192)
↓ Zinc in serum (0.77-fold) ↑ Chromium in serum (2.6-fold) ↓ Cobalt in serum ↓ Nickle in serum ↓ Iron in serum (0.47-fold)	50 AD & 50 control	ICP-MS	(193)
↔ Zinc in plasma (p = 0.36) ↓ Copper in plasma (0.87-fold, p=0.018)	16 AD & 13 control	Atomic Absorption Spectroscopy	(194)
↑ Copper in serum (p<0.001) ↑ Ceruloplasmin in Serum (p=0.052)	47 AD, 24 VAD, 44 controls	Atomic Absorption Spectroscopy	(195)
↔ Free Copper in serum (p=0.24) ↑ Cu/Ceruloplasmin in serum (p=0.01)	28 AD & 29 controls	Atomic Absorption Spectroscopy & enzymatic (eCp) and immunologic (iCp) methods	(196)

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Table 8. Vitamin and bio-metal AD biomarkers

Biomarker alteration in body fluid	Studied group	Method	Ref.
↓ Calcium in plasma (0.94-fold, p<0.0001) ↓ Hemoglobin in plasma (0.95-fold)	AIBL cohort: 754 controls & 207 AD ADNI cohort: 58 controls & 112 AD	ICP-MS & 151-analyte multiplex panel & sandwich ELISA	(88)
↔ Iron in serum (p=0.428)	28 AD, 13 MCI, 6 control (Taiwanese)	Flame atomic absorption spectrometry	(49)
↑ Heme oxygenase suppressor-1 (HOS) in plasma (AD: 2.7-fold, p < 0.001) ↑ α1-antitrypsin (AAT) in plasma (AD: p < 0.05)	46 AD, 13 PD, 30 MCI, 25 controls >60year, 9 control <60year	Glial bioassay for HOS activity & Turbidometric assay	(149)
↑ α1-antitrypsin (AAT) in plasma (~107-fold, *p* < 0.001) ↑ Transferrin in plasma (~5-fold, *p* < 0.001) ↑ Hemopexin in plasma (~6.5-fold, *p* < 0.001)	10 sporadic AD & 9 controls	Affinity chromatography & SDS-PAGE & Western blotting & MALDI-TOF MS	(197)
↑ α1-antitrypsin (AAT) in serum (*p* < 0.05)	45 early-stage AD & 20 control	ELISA & 2D gel electrophoresis combined with nano-HPLC-ESI-MS/MS	(94)
↓ Transferrin in serum (*p* < 0.05) ↑ Ferritin in plasma (p≤0.01) ↑ Ferritin in serum (p<0.05)	32 high NAL & 62 low NAL	Sandwich immunoassay using direct chemiluminometric	(198)
Positively associated with CSF Aβ1–42, p-tau, t-tau biomarker: Heavy metals (As, Cd, Hg, Ni, Pb, Tl) Essential metals (Ca, Co, Cu, Fe, Mg, Mn, Mo, Na, K, Zn) Essential non-metals (P, S, Se)	124 AD, 50 MCI, 19 control	ICP-MS	(187)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), PD (Parkinson disease), ICP-MS (Induction-coupled plasma mass spectrometry), NAL (neocortical amyloid-β load)

Blood cells

Blood cells are another matrix showed to reflect the health status of the brain. For example, the activated form of cyclic-AMP response element-binding protein (pCREB), which is involved in the formation of memories, reduces in the brain of AD patients. Bartolotti et al. have shown that the expression of this protein in peripheral blood mononuclear cells (PBMC) is correlated with its brain level according to the postmortem studies. It was claimed that the PBMC concentration of this protein can serve as a possible indicator of its expression level in the brain and thus "as a biomarker of cognitive function and disease progression in AD" (199). Seeking for biomarkers in blood cells has the advantage of less inter-individual variability due to dietary differences (in comparison to serum or plasma samples) and also less contamination (200, 201). Ren et al. investigated the PBMC miRNA changes in AD patients and proposed two miRNAs (miR-339 and miR-425) as potential biomarkers for AD with sensitivity and specificity of up to 80% (200). Using a whole platelet miRNA transcriptomics, Beyer and coworkers could have discriminated AD from dementia with Lewy bodies (202).

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As mentioned earlier, Aβ production is not limited to the CNS, peripheral cells like blood cells can also produce Aβ. The Aβ produced by platelets, is shown to induce AD phenotype in mice (29). The AD related biomarkers (APP, PS1 and PS2 mRNA; and PS1 and PS2 protein) are found in PBMC of obese subjects (203). The platelet APP form ratio is considered as a potential early diagnostic biomarker for AD with sensitivity and specificity of 88.2% of 89.4%, respectively (204). Neutral lipid accumulation in PBMCs (205), elevated coated-platelet levels (206), higher platelet-serotonin content (207), and increased platelet volume (208) are among the other blood cell changes reported in AD patients (Table 8).

Extracellular vesicles

Extracellular vesicles (EVs) including exosomes can originate from most cell types and can be isolated from multiple biofluids including urine, blood, or CSF (212). Some studies have introduced peripheral biomarkers based on EVs and their cargos that can be used for AD diagnosis and monitoring (Table 9) (213). For example, the exosomal level of $A\beta_{42}$, p-S396-tau, and p-tau181 has been shown to significantly increase in blood samples of AD patients (214-216).

Reduction of several exosomal synaptic proteins such as synaptophysin, synaptopodin, and neurogranin occurs early in normal aging and senile dementias, which can be used as early diagnostic marker for AD (215, 217). A decrease in some exosomal transcription factors which promote neuronal resistance against stresses is also reported in AD (216). Goetzl and co-workers showed that these factors could predict AD up to 10 years before clinical diagnosis (218).

Table 9. Blood cells-extracted AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
RBC			
↓ Mean cell hemoglobin concentration in RBC (0.99-fold, p< 0.0001)	207 AD & 754 controls	Multiplex panel (Human DiscoveryMAP)	(88)
Peripheral Blood Mononuclear Cells (PBMCs)-derived			
↓ pCREB in PBMCs (p=0.05)	> 1200 participants and > 600 autopsies (Only female)	Western blot	(199)
↑ fatty acid amide hydrolase (faah) in PBMCs (p<0.05) ↓ DNA methylation activity at faah gene promoter (p<0.05)	LOAD (23 females/ 9 males for DNA methylation studies and protein level detection, 13 for gene expression analysis), age- and sex-matched control (33 for DNA methylation studies and protein level detection, 12 for gene expression analysis)	HPLC	(209)
↑ Neutral lipids & ACAT-1 protein in PBMCs ↓ HDL cholesterol in plasma	93 probable AD and 91 their first-degree relatives vs. 57 CU and 113 blood donors as control	Oil red O (ORO) staining	(205)
↑ APP, PS1 and PS2 mRNA in PBMCs	45 middle-aged men	Real-time RT-PCR	(203)
↑ miR-339 in PBMCs ↑miR-425 in PBMCs	4 mild sporadic LOAD, 4 severe sporadic LOAD, 4 control	Microarray & Q-PCR	(200)

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Table 9. Blood cells-extracted AD biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ Pin1 mRNA in PBMCs (+74%; p = 0.018) ↓ Ser [16] phosphorylation (–30%; p =0.041) ↓ promoter methylation (–8%; p = 0.001)	32 LOAD (23 females/9 males), 28 age- and gender-matched control (19 females/9 males)	Chomczynski and Sacchi's modified method & real-time PCR	(209)
↑ Chitotriosidase mRNA in macrophages (~ 19-fold, p < 0.0001) ↑ IL-16 mRNA in macrophages (~21-fold, p < 0.0001) ↑ IL-18 mRNA in macrophages (~19-fold, p < 0.0001) ↑ TGF-β1 mRNA in macrophages (~32-fold, p< 0.0001) ↑ superoxide anion release from macrophages (~14-fold, p< 0.0001)	40 AD, 40 ischemic cerebrovascular dementias, 40 controls	Quantitative real-time polymerase chain reaction & Spectrophotometric measurement of ferricytochrome *c* reduction	(210)
↔ IL-1α in PBMCs ↑ IL-3 in PBMCs during MCI phase (p<0.05) ↑ IL-11 in PBMCs during MCI phase (p<0.01) ↑ EGF in PBMCs during MCI phase (p <0.05) ↔ G-CSF in PBMCs ↔ MCP-3 in PBMCs ↔ IL-6 in PBMCs	37 AD, 20 MCI, 9 Control	Searchlight mutiplex ELISA & Commercial single ELISA	(211)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), pCREB (cyclic-AMP response element-binding protein), LOAD (Late-Onset Alzheimer's Disease)

The onset and stage of AD may be reflected by miRNAs which are primarily found in nervous system. Recent studies have suggested that the brain miRNAs can cross the blood-brain barrier by transcytosis of exosomes and may be detected in biological fluids. Exosomes provide a protective shield against RNase-rich environments in circulatory system. Therefore isolating the enriched exosomal miRNA can enhance the chance of AD diagnosis (212).

Several laboratories have sought for differences in exosomal miRNAs expression between AD and non-AD subjects. Hill laboratory conducted a screening for miRNA sets to make a fingerprint for AD diagnosis. They identified a 16-miRNA signature extracted from serum exosomes which was specific for AD (144). Lugli et al. showed twenty miRNAs which were different in the AD group, among which a panel of seven miRNAs was highly informative (219). The most important miRNA was miR-342-3p that was reported in both studies (144, 219).

Insulin resistance is a disorder that is common between AD and type 2 diabetes mellitus. It is caused by abnormality in insulin receptor function, which is associated with more phospho-serine-type 1 insulin receptor substrate (P-serine 312-IRS-1) and less P-tyrosine-IRS-1. Kapogiannis et al. measured the ratio of these two proteins in plasma exosomes as AD biomarker. They showed that the ratio was significantly higher for AD patients compared with normal and even diabetes patient, and could 100% classify them (220).

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Despite evidence for blood based exosomal biomarkers to be a promising and complementary tool for AD prediction (144, 212), there is a concern about the relevance of blood extracted exosomes that can originate from all others organs instead of CNS. Goetzl and co-workers offer a novel approach to increase specificity of these biomarkers. They extract brain-derived exosomes in blood samples using anti L1 cell adhesion molecule (L1-CAM) antibodies (217, 218), and could remove the noises generated from whole bloodstream exosomes. Although this approach was developed in order to be brain-specific, L1-CAM is also expressed in the renal system; therefore the interpretation of the results should be done with caution (221). Fiandaca et al. compared Neural Cell Adhesion Molecule 1 (NCAM-1) to L1-CAM for enrichment of neuron-derived exosomes in blood samples. These cell adhesion molecules are differently distributed in the nervous system, however the difference between extracted exosomal p-tau181, P-S396-tau, total tau, and $A\beta_{42}$ were statistically insignificant whether enriched with anti-NCAM-1 or anti-L1CAM antibodies (214).

In another study, Goetzl et al. used astrocyte cell surface antigen-1 (ACSA-1) to isolate astrocyte-derived exosomes. They observed that the levels of $A\beta_{42}$-generating system factors (BACE-1, sAPPb and septin-8) and neuronal trophic-survival factor (GDNF), a small protein involved in neuron survival, can significantly be altered in astrocyte-derived exosomes (but not in neuron-derived ones) of AD patients in comparison to controls (222).

The effect of autophagocytic-lysosomal dysfunction in pathophysiology of AD has been emphasized in recent years. Goetzl et al. suggested that the enhancement of lysosomal components (cathepsin D, LAMP-1 and ubiquitinylated proteins) and reduction of HSP-70 can be biomarker candidates for AD diagnosis (223).

Table 10. Blood-extracted Extracellular Vesicles-related AD Biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
↑ Aβ1-42 in Blood ↑ P-S396-tau in Blood ↑ P-T181-tau in Blood	57 AD, 16 FTD, 24 CU that 1-10 years later diagnosed with AD	Enrichment of Neuronal derived exosome by NCAM-1 and L1CAM	(214)
↑ Aβ1-42 in plasma ↑ P-S396-tau in plasma ↑ P-T181-tau in plasma ↓ neurogranin in plasma ↑ REST in plasma	10 CU, 10 AD, 20 stable MCI, 20 transitioned from MCI to AD within 36 months	Enrichment of Neuronal derived exosome by L1CAM	(215)
↑ Aβ1-42 in plasma ↑ P-T181-tau in plasma ↑ Cathepsin D (Lysosomal proteins) in plasma ↓ neurogranin in plasma	20 volunteers (≥60) (samples collected at 3- to 11-year intervals)	Enrichment of Neuronal derived exosome by L1CAM	(216)
↑ BACE-1 in plasma ↑ sAPPb in plasma ↓ septin-8 in plasma ↓ GDNF (Neurotropic factors) in plasma	12 AD, 14 FTD, 20 control	Enrichment of Neuronal derived exosome by ACSA-1	(222)
Lysosomal proteins: ↑ Cathepsin D in Blood ↑ LAMP-1 in Blood ↑ Ubiquitinylated proteins in Blood ↓ HSP 70 in Blood	26 AD,16 FTD, 20 control which 1 to 10 years later diagnosed with AD	Enrichment of Neuronal derived exosome by L1CAM	(223)

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Table 10. Blood-extracted Extracellular Vesicles-related AD Biomarkers.

Biomarker alteration in body fluid	Studied group	Method	Ref.
Insulin resistance factor (R): ↑ P-serine 312-IRS-1/ P-pan-t yrosine-IRS-1 ratio in plasma	26 AD, 20 DM2, 16 FTD, 22 control which 1 to 10 years later diagnosed with AD	Enrichment of Neuronal derived exosome by L1CAM	(220)
Synaptic proteins: ↓ Synaptophysin in plasma ↓ Synaptopodin in plasma ↓ synaptotagmin-2 in plasma ↓ neurogranin in plasma ↓ growth-associated protein 43 in plasma ↓ synapsin 1 in plasma	Cross-sectional study: 12 AD, 16 FTD, 28 controls Longitudinal study: 9 AD, 10 FTD, 19 controls	Enrichment of Neuronal derived exosome by L1CAM	(217)
Transcription factors: ↓ LRP6 ↓ HSF1 ↓ REST	24 (cross-sectional studies), 16 (longitudinal studies), 10 FTD	Enrichment of Neuronal derived exosome by L1CAM	(218)
↑ MicroRNA in serum: has-MiR-101.3p, has-MiR-106.a5p, has-MiR-106b.5p, has-MiR-1306.5p, has-MiR-143.3p, has-MiR-15a.5p, has-MiR-15b.3p, has-MiR-18b.5p, has-MiR-20a.5p, has-MiR-30e.5p, has-MiR-335.5p, has-MiR-342.3p, has-MiR-361.5p, has-MiR-424.5p, has-MiR-582.5p, has-MiR-93.5p	Discovery test: 23 CU, 3 MCI, 23 AD Validation test: 36 CU, 8 MCI, 16 AD	-	(144)
↑ MicroRNA in plasma miR-23b-3p, miR-24-3p, miR-29b-3p, miR-125b-5p, miR-138-5p, miR-139-5p, miR-141-3p, miR-150-5p, miR-152-3p, miR-185-5p, miR-338-3p, miR-342-3p, miR-342-5p, miR-548-5p, miR-659-5p, miR-306-5p, miR-3613-3p, miR-3916, miR-4772-3p, miR-5001-3p	35 AD & 35 control	-	(219)

AD (Alzheimer's disease), CU (cognitively unimpaired), MCI (mild cognitive impairment), FTD (frontotemporal dementia), REST (repressor element 1-silencing transcription factor), DM2 (type 2 diabetes mellitus), LRP6 (low-density lipoprotein receptor-related protein 6), HSF1 (heat-shock factor-1),

Conclusion

The importance of early diagnosis of AD in the prevention of disease progression and treatment success is evident today and thanks to technological advances, the role of biomarkers is expanding in this field. Among the different categories of biomarkers, blood-based biomarkers (BBBs) are promising due to their ease of access that provides the possibility of multiple sampling with low cost and less invasion.

However, no single biomarker has shown to be robust enough to diagnose AD with reliable sensitivity and specificity. Considering the complexity and heterogeneous nature of AD, simultaneous assessment of multiple biomarkers, not necessarily interrelated, may enhance the possibility of attaining a more reliable sensor array. Currently, p-tau218 is among the most promising diagnostic plasma biomarkers, in addition to, neurofilament light (NfL), p-tau181, and $A\beta_{42}/A\beta_{40}$ ratio. It seems that application of these BBBs would be a big step towards detection of AD in early stages.

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Despite the efforts made so far, inconsistency of results among various studies remains a main challenge to be addressed. In addition to demographic characteristics, diet, health condition, and comorbidities, the profile of BBBs may also be affected to some extent by pre-clinical and analytical steps. Multiplexing as a method for simultaneous detection of an array of suitable biomarkers from different categories may overcome the inter-individual variability and enhance the chance of early diagnosis.

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