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REVIEW ARTICLE

Can blood amyloid levels be used as a biomarker for Alzheimer's disease?

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ABSTRACT

Alzheimer's disease (AD) increasingly affects society due to aging populations. Even at pre-clinical stages, earlier and accurate diagnoses are essential for optimal AD management and improved clinical outcomes. Biomarkers such as beta-amyloid (Aβ) or tau protein in cerebrospinal fluid (CSF) have been used as reliable markers to distinguish AD from non-AD, and predicting clinical outcomes, to attain these goals. However, given CSF access methods' invasiveness, these biomarkers are not used extensively in clinical settings. Blood Aβ has been proposed as an alternative biomarker since it is less invasive than CSF; however, sampling heterogeneity has limited its clinical applicability. In this review, we investigated blood Aβ as a biomarker in AD and explored how Aβ can be facilitated as a viable biomarker for successful AD management.

1 Alzheimer's disease

Globally, Alzheimer's disease (AD) severely affects society due to increased aging populations and has become the most prevalent cause of early-onset or late-onset dementia [1]. Its pathological journey commences at pre-clinical stages and is characterized and identified by sequential changes from neuroimaging. Changes in morphology are observed in brain areas susceptible to pathological changes, concomitant with abnormal protein or peptide formation and

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deposition. Such abnormal protein and amyloid deposits lead to an impaired cytoskeleton and phosphorylated or non-phosphorylated tau proteins, which affect neuron function and disease presentation [2]. Amyloid and tau protein biomarkers can be determined in cerebrospinal fluid (CSF) or blood to reflect the disease stage [3–5]. During the early clinical presentation, subtle memory or cognitive functions may decline or change, suggesting abnormal pathogenesis may have already commenced decades earlier. Effective therapies implemented by physicians who can detect very mild or early dementia changes are essential to modify disease processes and prevent profound impairment.

Current and upcoming clinical trials have focused on pre-symptomatic individuals, either harboring cerebral amyloid or at high genetic risk, to ameliorate AD symptoms and modify early stage AD to address AD clinical issues. Therefore, more robust biomarkers are required to ensure objective and measured changes during early clinical stages.

2 AD pathogenesis

Two neuropathological hallmarks characterize AD: amyloid plaques of varying amyloid peptide lengths and neurofibrillary tangles (NFT) comprised of tau proteins that impair the cytoskeleton [6, 7]. Morphologically, amyloid plaques are described as either diffuse or neuritis and may occur in individuals with or without dementia. Potentially, they indicate an increased progression risk to dementia, or advanced stages, ranging from mild dementia or pre-clinical dementia stages. However, amyloid deposition in the AD brain is not significantly associated with clinical severity [8, 9].

In contrast to NFT, amyloid plaque distribution usually begins in the neocortical regions, mostly in the hippocampus, temporal or frontal areas, in early dementia stages with eventual progression to other cerebral cortex areas [7]. The disease develops by progressively increasing subcortical deposits with eventual brainstem and cerebellar involvement, but the deposition rate may sometimes decline and reach a plateau in the late stages of dementia [8]. Therefore, some individuals without clinical dementia symptoms may exhibit significant amyloid or tau levels by positron emission tomography (PET). Ligands against amyloid and tau proteins have greatly facilitated molecular imaging and identified real-time neuropathological changes and disease evolution.

3 The origins of β-amyloid (Aβ)

Amyloid peptides form via amyloid precursor protein (APP) cleavage at several enzyme sites. Currently, brain amyloid peptides and APP's precise roles are unclear, but they have potential roles in AD pathogenesis and treatments [10]. The APP gene is ancient and indispensable to the amyloidogenic sequence to the proposition of having AD and is found in all vertebrates [11]. It is also essential for neuronal development. In animal studies, APP gene knockouts in mice are usually lethal [12].

Non-amyloidogenic and amyloidogenic pathways characterize the amyloid peptide formation process by APP. In the former, which occurs during normal aging, APP is mostly cleaved in the cell membrane by α-secretase in the Aβ peptide region of APP, to release the soluble fragment, α-APP ($A\beta_{1-40}$) into the extracellular space. In the brain, α-APP levels are particularly high in subventricular zones, situated on the outside wall of each lateral ventricle of the vertebrate brain [13]. These zones are present in both embryonic and adult brains and contain neural progenitor cells that produce neurons during

neurogenesis [14]. Thus, α-APP is an essential proliferation factor for stem cells [15].

In contrast, the amyloidogenic pathway leads to AD. APP is cleaved by β-secretase at a different Aβ peptide region, releasing soluble β-APP to the extracellular space. β-APP also drives stem cells toward neural differentiation [16]. The soluble peptides, α-APP and β-APP, are generally produced in a proximal 9:1 ratio and simultaneously stimulate neural stem cell proliferation and differentiation [17].

After APP cleavage to release β-APP, the remaining membrane-bound APP C-terminal is subsequently cleaved by γ-secretase, to release insoluble $A\beta_{1–42}$ peptide into the extracellular space, leaving the APP intracellular domain. Consequently, synaptic activity is affected by $A\beta_{1–42}$ due to aggregation and toxicity effects [18, 19]. Equally, inflammatory effects generated by cellular dysfunction trigger tau protein hyper-phosphorylation, which is implicated in AD pathogenesis [20].

4 The effects of APOE4 on plasma $A\beta_{1–42}$ and $A\beta_{1–40}$ levels

Apolipoprotein E4 (APOE4) allele carriers have an increased risk for AD; however, it is unclear how these carriers are associated with plasma amyloid levels and AD. A recent study suggested APOE4 carriers had significantly reduced soluble low-density lipoprotein receptor-related protein-1 (sLRP1) levels, predisposing these carriers to AD. Plasma sLRP1 binds 70%–90% of peripheral amyloid protein, preventing its access to the brain to increase the possibility of having AD [2, 20–22]. A recent study recruited 1119 normal cognitive and 24 cognitive impaired subjects to address this issue. The study found significantly higher $A\beta_{1–42}$ plasma levels but not $A\beta_{1–40}$ in APOE4 carriers when compared with non-carriers [23].

These relationships were, in part, different in mild cognitive impairment (MCI) or AD patients. In patients with MCI, plasma $A\beta_{1–40}$ and $A\beta_{1–42}$ levels were not different concerning their APOE4 carrier status and AD group [24]. MCI patients with APOE4 carrier status, when compared with non-carriers, had significantly greater decreased plasma $A\beta_{1–40}$ and $A\beta_{1–42}$ levels after three years in a longitudinal study [24, 25].

Our previous study, which examined dynamic changes using a series of measurements in a sample of plasma $A\beta_{1–40}$ and $A\beta_{1–42}$ in AD patients, has found for the plasma $A\beta_{1–42}$, the APOE4 carrier had a significantly lower level than the non-carriers at baseline {31.2 ± 6.5 ng/mL *vs.* 50.4 ± 47.7 ng/mL [mean ± standard deviation (SD)], $p = 0.031$} and the 0.5 h (37.5 ± 7.6 ng/mL *vs.* 51.9 ± 30.8 ng/mL, $p = 0.043$), but the differences were not significant in other time-points, 1, 2, 3, 5, 8, and 24 h (all $p > 0.05$). For $A\beta_{1–40,}$ levels at each checkpoint were not significantly different by APOE4 carrier status (all $p > 0.05$) [26].

From these findings, the association of APOE4 and plasma $A\beta_{1–40}$ and $A\beta_{1–42}$ levels may be related to AD, AD severity, hemoglobin, platelet, peripheral clearance capabilities, and others [24, 26]. These factors in plasma also will cause different $A\beta_{1–40}$ and $A\beta_{1–42}$ levels in CSF and require different detection methods, such as the alternative enzyme-linked immunosorbent assay (ELISA) assays, AB*test*42 and AB*test*40 (Araclon Biotech Ltd., Zaragoza, Spain). In these methods, plasma was pre-treated to disrupt interactions between Aβ peptides and other plasma components.

5 CSF and plasma amyloid levels in the clinical course of AD

AD biomarkers must be thoroughly investigated and characterized to trace the clinical course of

disease, enhance diagnostic accuracy, and increase our understanding of AD mechanisms. Given the effects of the amyloid pathway on AD development, CSF and neuroimaging measures, which determine amyloid levels, potentially reflect AD pathology and are thus major disease indicators.

CSF total tau, phosphorylated tau, and amyloid protein biomarkers reliably distinguish patients with AD from non-AD controls [27]. Moreover, for amyloid protein, the application of CSF $A\beta_{1–42}$, $A\beta_{1–40}$, and $A\beta_{1–42}$ /$A\beta_{1–40}$ ratios, or other amyloid peptides, are potential biomarkers delineating AD from non-AD cases, often with acceptable outcomes [28–30]. However, fluctuating CSF amyloid levels have been variably demonstrated and are affected by several factors, including sleep [31], and where average maximum values were 200% those of minimum values [32]. These amyloid fluctuations and dynamic changes in CSF or blood level measurements, together with different clinical diagnostic criteria of study AD patients, complicates amyloid measurements, especially when different laboratory procedures, sample preparations, and methods are used. These variations, therefore, highlight the requirement for methodological standardization across the field [33].

Changes in Aβ plasma levels may reflect changes in the brain [34, 35], but may also be more affected by other plasma factors. Overproduction or decreased clearance of Aβ has been associated with AD development. Aβ overproduction leads to AD development in subjects with familial AD or Down syndrome, where plasma Aβ levels often begin to increase before dementia onset [36–38]. Decreased plasma Aβ clearance has also been reported in sporadic or late-onset AD, although a plasma Aβ clinical assay has demonstrated inconsistent results [4]. Plasma Aβ levels have reportedly increased before dementia onset in familial AD patients or Down syndrome due to the increased production of Aβ in these patients [3, 37, 38], but these associations are not reported in sporadic or late-onset forms of AD with enough evidence.

Relationships between plasma $A\beta_{1–40}$, $A\beta_{1–42}$ and dementia vary between studies [5, 39, 40]. Some have observed associations between lower $A\beta_{1–42}$/$A\beta_{1–40}$ ratios and a higher risk of AD [41, 42], whereas others reported no association [34]. Such variations in plasma Aβ levels relative to clinical disease are because of variability in subject age, study design, plasma quality, and storage for Aβ quantification or disease severity [43, 44].

A previous study examined plasma Aβ correlations with AD and observed plasma $A\beta_{1–42}$ ($p = 0.01$) and $A\beta_{1–40}$ ($p = 0.04$) levels were lower in AD (mean ± SD; 36.9 ± 11.7 and 263 ± 80 pg/mL, respectively) than amnestic MCI (38.2 ± 11.9 and 269 ± 68 pg/mL, respectively) and non-amnestic MCI (39.7 ± 10.5 and 272 ± 52 pg/mL, respectively), after control age, educational level, sex, having APOE4 carrier [45]. This study also suggested that plasma $A\beta_{1–42}$ and $A\beta_{1–40}$ levels decreased relative to cognition severity. AD was in an advanced stage of impaired cognition compared with amnestic and non-amnestic MCI [46]. But the association between advanced cognition, AD stage, and plasma $A\beta_{1–42}$ and $A\beta_{1–40}$ levels cannot be duplicated in our study examined the plasma $A\beta_{1–42}$ and $A\beta_{1–40}$ level in different AD stages, very mild stage versus advanced stage. AD patients at very mild stages have significantly lower plasma $A\beta_{1–40}$ levels ($p = 0.010$), but not $A\beta_{1–42}$ ($p = 0.691$) when compared with advanced stage levels [26].

In addition to examining plasma $A\beta_{1–42}$ or $A\beta_{1–40}$ levels separately (often heterogeneous results), the $A\beta_{1–42}$/$A\beta_{1–40}$ ratio was introduced and has found it decreased as amyloid-PET

binding increased. The ratio has been considered a screening method to detect very mild stage dementia concerning cognitively normal individuals [47].

Recently, several newly-developed methods have increased diagnostic efficacy by reflecting cerebral amyloid load, by amyloid-PET, through blood amyloid level. The ultrasensitive single-molecule array (SIMOA) quantifies plasma amyloid ratios [47]. Also, improved ELISA formats have shown promising clinical performances [48]. Both ELISA and SIMOA methods detect plasma $A\beta_{1–42}/A\beta_{1–40}$ ratios with identical accuracy; ELISA area under curve (AUC) = 0.78, 95% CI 0.72–0.84 and SIMOA AUC = 0.79, 95% CI 0.73–0.85. ELISA and SIMOA have positive predictive values of 41% and 36%, respectively, and negative predictive values of 96% and 94%, respectively, in cognitively normal elderly individuals [47].

Briefly, although the introduction of new detecting methods, some studies were unable to replicate findings in other sites with introducing controversy and casting doubts on the reliability of blood-based biomarkers. These issues were derived from the current understanding of Aβ peptide interactions within the complex plasma matrix and gap between positive amyloid-PET findings and having clinical dementia. If we used cortical amyloid status instead of a clinical diagnosis of dementia as the gold standard to assess Aβ blood-based biomarkers, the gap and differences would be minimized to reduce data heterogeneity.

6 The benefits of plasma amyloid levels

Given the CSF procedure's invasiveness in routine practice, plasma Aβ levels are more convenient and applicable as biomarkers. While there is communication between the peripheral and central Aβ level pools through several mechanisms, including several circulation enzymes such as the angiotensin-converting enzyme, that can directly degrade Aβ, microglial phagocytosis, or transport from the brain to the blood via the blood–brain barrier, arachnoid villi and blood–CSF barrier. Because of these communications, after the Aβ circulated to peripheral blood, the clearance system will be responsible for its clearance. Meningeal lymphatic vessels can also help with lymphatic clearance, with key roles in Aβ transport into cervical lymph nodes, also known as the lymphatic clearance pathway [49]. The current data suggest plasma Aβ levels are difficult to characterize due to their inherent metabolic interactions.

Although plasma Aβ measurements' utility is limited, with often inconsistent results, studies have reported correlations between plasma Aβ levels and dementia risk and/or progression. Apart from cross-sectional studies which examine plasma Aβ levels in a case-control study, the longitudinal examination of Aβ level changes in relation to the clinical course is necessary. Intra-individual comparisons of plasma Aβ level changes in longitudinal studies can minimize confounding factors and increase our understanding of the clinical application of plasma Aβ to disease etiology.

7 Pitfalls in detecting amyloid plasma levels

Compared with CSF, plasma Aβ levels are evolving as viable predictors of developing dementia for late-onset AD; however, findings are often inconsistent. Results from longitudinal studies using plasma $A\beta_{1–40}$ or $A\beta_{1–42}$ levels as AD predictors are varied [5, 9, 39, 40]. In contrast to using plasma $A\beta_{1–40}$ or $A\beta_{1–42}$ levels alone, more consistencies have been observed when using the $A\beta_{1–42}$ /$A\beta_{1–40}$ plasma ratio. Those

non-demented patients will have a higher risk of AD with their lower $A\beta_{1–42}$ /$A\beta_{1–40}$ ratios [41, 42]. In terms of predicting whether patients with MCI will convert to AD, no consistent data on plasma $A\beta_{1–42}$, $A\beta_{1–40,}$ or ratios have been reported [9, 39, 40].

Data variability is often due to sampling variability regarding subject age and/or disease severity [39, 44], but may also be related to plasma Aβ levels, e.g., an individual's peripheral clearance of Aβ [50], hemoglobin levels [25], apolipoprotein E genotype [26], or platelet levels [51]. Whether age is a factor to plasma amyloid level, the association of age and increased plasma Aβ and reduced $A\beta_{1–40}$ / $A\beta_{1–42}$ ratio was primarily restricted to MCI patients or individuals with worsening cognitive status [9].

8 Dynamic changes in plasma $A\beta_{1–42}$ and/or $A\beta_{1–40}$ levels

Recently, we assessed plasma $A\beta_{1–40}$ and $A\beta_{1–42}$ levels using a particular study design to explore possible changes in $A\beta_{1–40}$ and $A\beta_{1–42}$ levels after leaving from the peripheral blood vessel. Previous studies indicated factors in peripheral blood that contributed to $A\beta_{1–40}$ and $A\beta_{1–42}$ plasma concentrations after blood samples were taken. To examine the unstable characteristics or dynamic changes in plasma $A\beta_{1–42}$ and $A\beta_{1–40}$ levels in blood samples, we used fresh blood in ethylenediaminetetraacetic acid tubes from 32 clinically diagnosed AD patients and performed eight continuous measurements, with a scheduled time point for each sample. Each blood sample was subdivided into eight sub-samples, by time at 0 (baseline), 0.5, 1, 2, 3, 5, 8, and 24 h, to simultaneously measure plasma $A\beta_{1–40}$ and $A\beta_{1–42}$ levels. All samples were incubated at 37 °C to mimic human body temperature before measuring.

When compared to each sample's baseline level, 87.5% and 62.5% of samples, individuals had higher $A\beta_{1–42}$ and $A\beta_{1–40}$ plasma levels at 24 h, respectively. $A\beta_{1–42}$ and $A\beta_{1–40}$ levels at each checkpoint were significantly different [26]. These findings indicated that $A\beta_{1–42}$ and $A\beta_{1–40}$ plasma levels continuously changed. This study illustrated the dynamic nature of plasma $A\beta_{1–42}$ and $A\beta_{1–40}$ levels by time, reflected the situation of human blood, and highlighted the importance of time interval effects between sample preparation and measurement. These should be taken into consideration in coming measurements.

9 Blood processing times for checking $A\beta_{1–42}$ and $A\beta_{1–40}$ plasma levels

The Alzheimer's Disease Cooperative Study (ADCS) centrally processed blood samples to reduce variations in pre-analytical handling [52]. Whole blood samples were shipped overnight in ambient temperature gel packs and processed at approximately 24 h post-draw. The statement was supported by a study that evaluated stability by assessing time-to-processing effects and demonstrated that plasma $A\beta_{1–40}$ (mean ± SD) decreased from 267 ± 46 pg/mL at 0 h to 190 ± 41 pg/mL at 24 h, and 143 ± 33 pg/ml at 48 h, or an average decrease of approximately 2.6 pg/mL per hour [53]. Similarly, $A\beta_{1–42}$ levels decreased from 29 ± 4 pg/ml at 0 h to 2 ± 4 pg/mL at 24 h, and 19 ± 3 pg/mL at 48 h, or an average decrease of approximately 0.2 pg/mL per hour [53]. The ADCS concluded that blood processing should be performed within 24 h to minimize artificial results. In contrast, another similarly conducted study reported that $A\beta_{1–42}$ plasma concentrations were stable in whole blood processed as much as 24 h after collection [54].

Actually, whatever results, increased, decreased, or stable, have been reported after or within 24 h for plasma Aβ measurement, the dynamic change of plasma Aβ always challenged these

measurements [26]. We recommend all methods have their own standard procedures and their results concerning clinical significance to minimize the effects of different laboratories.

10 Conclusions

With improvements in $A\beta_{1-42}$, $A\beta_{1-40}$ plasma level assay, or other amyloid peptides in the increased sensitivity, specificity, and accuracy, and better correlation to disease diagnosis and clinical outcomes, the plasma amyloid peptides have shown their potentials in clinical application, especially for more understandings of their correlations to disease. Sample processing for each detection method must be standardized in combination with specific clinical applications. When sample processing procedures are established, scientifically sound experimental designs and analyses that control confounding factors, such as age, renal function, platelet levels, genetic factors, or others, must be performed to ensure Aβ is a useful, reliable biomarker. Only then can we facilitate disease-modifying therapies for AD and monitor the clinical course with less invasive methods.

Conflict of interests

The authors declare that they have no conflict of interests.

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