Blood biomarkers for Alzheimer's diseases: moving towards to the early and non-invasive diagnosis.

Adriana Poza Rodríguez

Abstract

Alzheimer's disease (AD) is major challenge for today's society due to the increasing number of patients and the lack of a definitive cure. Nowadays, there are disease-modifying therapies that delays the devastating symptomatology when given on time. Therefore, there is a need for an early and accurate AD diagnosis, that could be achieved by using biomarkers. Currently, there is an increase interest in AD blood biomarkers due to their low cost and invasiveness and high efficiency and efficacy in diagnosis. Here, we reviewed the most recent updates about blood AD biomarkers, focusing on the different forms of amyloid β and Tau protein, and examined their diagnostic accuracy . With all the collected data, we implemented an integrated model that suggest when these biomarkers can be detected thought the preclinical stages, facilitating the clinical intervention against AD. Finally, we reflected about future of blood AD biomarkers, discussing their limitations and challenges that need overcome, and highlighting their enormous potential as diagnostic, clinical and research tools.

Layman's Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that affects a large part of the population. Even though there is not a current cure for AD, there are some therapies that can slow down the progression of the disease and ease its severe symptoms. This therapies have to start as soon as possible, even before the first symptoms appear. The main problem is that, patients already manifest AD symptomatology when they receive a definitely AD diagnosis. By this time, it is already late to administer a drug as the brain is severely damage. For this reason, there is an urgent need for methodologies that make possible to detect AD before the symptoms appear. This is where biomarkers come into play. Biomarkers are molecules that are used as a tool to assess the presence and the progress of a disease. In AD there are two main proteins function as biomarkers, amyloid β and Tau protein, because they change thought the development of the disease. Currently, there are different techniques and body fluids that helps clinicians and researchers to detect and monitor these proteins, but the most appealing are blood related. This is because extracting and processing blood is less invasive and cheaper than other methods like brain imaging or cerebrospinal fluid analysis. Here, we gathered the latest information available about blood biomarkers for diagnosing AD and designed a model that reflects what blood biomarker can be detected, in which stage of AD can be detected and how can be detected. In this way, we

can help researchers and clinicians to make an accurate diagnosis and give an effective intervention on time. Lastly, we exposed their limitations and challenges because AD blood biomarkers are very recent tools. Still, we remarked the powerful tools that biomarkers represent for getting an early AD diagnostic.

Keywords: Alzheimer's diseases, early diagnosis, biomarkers, blood, amyloid β, Tau protein

Abbreviations: AD, Alzheimer's disease**; Aβ,** amyloid β**; APP,** amyloid precursor protein**; AT(N),** amyloid, tau (neurodegeneration); **CSF,** cerebrospinal fluid**; PET,** positron emission tomography**; P-tau,** phosphorylated tau**; T-tau,** total Tau.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that represents one of the leading forms of dementia. Worldwide, 55 million people are affected by dementia from which the 60-70 % are cases of AD (WHO, 2023). As the population ages, the number of patients increases, estimating that it will triplicate by 2050 (WHO, 2023). AD is characterised by a progressive loss of the brain functionality and structure (reviewed in Martin, 1999). This brain deterioration is associated to the presence of amyloid fibrils, which are abnormal deposits of proteins aggregates (reviewed in: Mandelkow & Mandelkow 1998; Soto, 2003; Chiti & Dobson, 2017; Erkkinen, Kim & Geshwind, 2018; Naseri et al., 2019). In the case of AD, there are two main hallmarks: extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles of the protein Tau.

Currently, there is no cure for AD. One of the reasons behind this is that the molecular mechanisms underlying AD is still unknown. Nevertheless, there are disease-modifying therapies that delay the development of the disease (Cummings & Fox, 2017). The most promising ones are treatments based on using synthetic peptides or monoclonal antibodies to clear protein aggregates from the brain (Barrera-Ocampo & Lopera, 2016; Valiukas et al. 2022). Some recent treatments are Aducanumab (Padda & Parmar, 2021), Lecanemab (Swanson et al. 2021; Pasieka et al. 2023) or Donanemab (Eli Lilly and Company, 2023). Specifically, these three treatments are monoclonal antibodies that target and clear Aβ plaques (Padda & Parmar, 2021; Swanson et al. 2021; Eli Lilly and Company, 2023). Still, these treatments are highly controversial among the scientific community. Among other concerns, the most highlighted ones are the appearance of some side effects, like microhaemorrhages (Wojtunik-Kulesza, Rudkowska & Orzel-Sajdlowska, 2023) or the lack of evidence in *postmortem* brains that proves the reduction of the amyloid plaques after the treatment (Golde, 2022). In any case, the US Food and Drug Administration (FDA) already approved two of these drugs (Aducanumab (de la Torre & Gonzalez-Lima, 2021) and Lecanemab (Mahase, 2023)), and it is in the process of approving the third one (Donanemab (Fitzgerald, 2024)) due to the great advance that they represent for AD treatment. Several studies suggest that these treatments are more effective when administered in the early stages of the disease (McDade & Bateman 2017; Polanco et al. 2018; Sims et al. 2023; van Dyck et al. 2023), having great impact in the life of the patients, improving cognitive functions, functional decline, and behavioural changes (Gauthier, 2005; Jouanne, Rault & Voisin-Chiret, 2017). This could only be achieved

throughout an accurate and early AD diagnosis. Currently, AD is diagnosed through techniques that demand clear clinical manifestation and neuropsychological test (Wu et al. 2017). Furthermore, a definitely AD diagnosis also requires presence both amyloid plaques and neurofibrillary tangles of Tau protein (McKhann et al. 2011). In some cases, this neuropathological analysis could only be done in the brain at death. For early AD diagnosis this represents an obstacle, as the symptomatology manifestations occurs 20 years later the aggregation process start (Bateman et al. 2012; Villemagne et al. 2013; Gordon et al. 2018; Self & Holtzman, 2023). Therefore, there is a strong need to develop tools that allows to diagnose AD early.

Nowadays, an early diagnosis of AD can be achieved by using biomarkers. By definition, a biomarker is an analytical tool that quantifies and evaluates a biological parameter (Biomarkers definitions working group, 2001). Thus, a biomarker reflects the normal or abnormal values of a process (National Cancer Institute, 2023)**,** allowing *in vivo* and e*x vivo* analysis with no need of symptomatology manifestation. For AD, biomarkers are grouped in cerebral amyloidosis (A), tauopathy (T) and neurodegeneration (N), resulting in the framework AT(N) (Jack Jr et al. 2018; Burke et al. 2018). AT biomarkers are regularly used for diagnostic purposes, as the molecules that are involve in the development of the disease are directly measured. Inside the A group it is typically measured APP, Aβ40, Aβ 42, ratio Aβ42/40 while in T group, total Tau content (t-tau) or different phosphorylated Tau isoforms (p-tau). Remarkably, these biomarkers, besides from being diagnostic tools, they are used to determine the state and the progression of the disease that, ultimately, affects the clinical decisions (Budd haeberlein et al. 2022; van Dyck et al 2023; Eli Lilly and Company, 2023). For these reasons, there is an increased interest to further study and develop these incredible versatile tools. In fact, since 2019, there is double of literature about AD biomarkers (Blennow et al. 2023). Hence, being updated about what biomarkers can be used, how and where they can be identified and at which state of the disease can be detected is crucial for the early AD diagnosis (Fig 1).

The aim of this review is to collect information about the biomarkers, around the AT framework, and techniques used for AD diagnosis. For this, we discuss from the historical point of view of the biomarkers, from past to future. We present information about the most used techniques and samples until now. Here, we also gather the latest implementations of AD biomarkers evaluated with non-invasive techniques, in this case

through blood sampling. Taking all of these into account, we update the integrated model designed by Zetterberg & Bendlin (2021). Finally, we reflect about the future role of the biomarkers, discussing the remaining challenges and highlighting their importance in early AD diagnosis and it's use in clinic procedures.

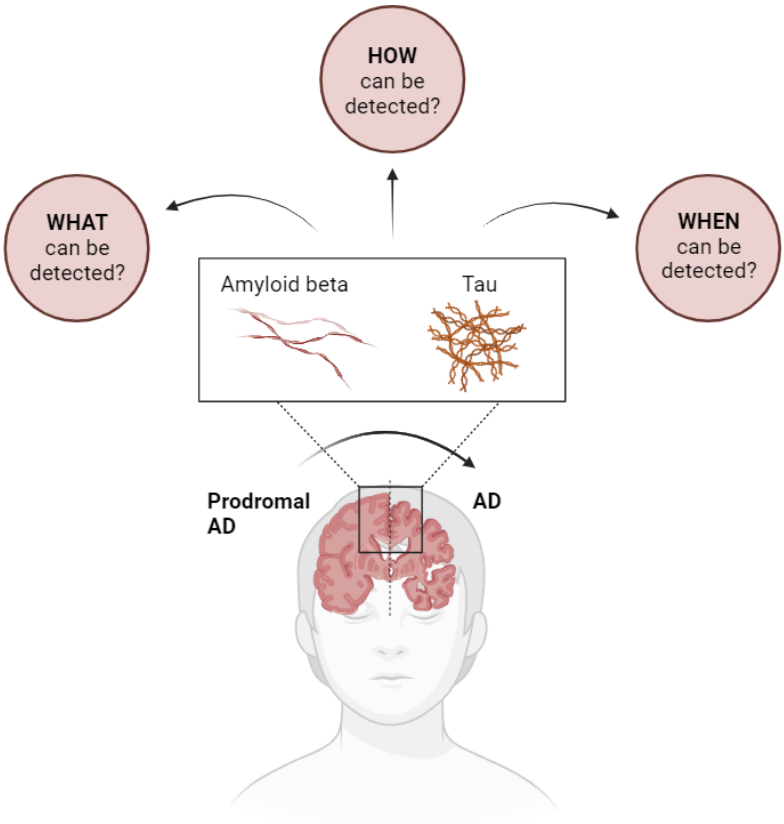

***Figure 1**: AD biomarkers. The figure illustrates the core biomarkers for AD, amyloid beta and tau. These two biomarkers appear in preclinical stages of the diseases, stablishing the challenge in what can be detected of AD, how it can be detected and when it can be detected.*

1. Past: what have we been doing until now?

The interest in having an early diagnosis for AD starts in the late 90's, when different biological markers were proposed to identify prodromal AD, *in vivo* and before an autopsy (The Ronald and Nacy Reagan Research Institute of the Alzheimer's Association & National Institute on Aging Working Group, 1998; Growdon, 1999). Since then, several tools were developed, principally neuroimaging techniques or immunoassays for CSF samples to support the AD diagnosis (Cohen et al. 2019)

1.1 Neuroimaging biomarkers

According to the Alzheimer's Disease Neuroimaging Initiative (Veitch et al. 2023) there are two main neuroimaging techniques used in AD diagnosis: magnetic resonance

imaging (MRI) and positron emission tomography (PET). In essence, MRI is used to characterise the degree of neurodegeneration, while PET measures the direct biomarkers of AD (Aβ and Tau), making this technique object of this review.

The PET is based in the use of a radiotracer, a radioactively labelled molecule that binds to a protein of interest. PET has been widely used to measure Aβ plaques (Rowe et al. 2008; Nelissen et al. 2009; Newberg et al. 2012; Betthauser et al. 2019; Cohen et al. 2019). In clinic, there are three radiotracers approved by both the European Medicines Agency (EMA) and the FDA that are extensively used for AD diagnosis: Amyvid, Vizamyl and Neuraceq (Zetterberg & Bendlin, 2021). There is a fourth radiotracer, ^{11}C-PIB, which use has been limited to research due to its' brief half-life (Klunk et al. 2004; Ikonomovic et al. 2008; Zetterberg & Bendlin, 2021). Despite this, ^{11}C-PIB plays a critical role in the clinical trials, tracking the effects of drugs that target Aβ fibrils (Nordberg et al. 2010) and, moreover, to assess new biomarkers (Zetterberg & Bendlin, 2021). Tau radiotracers are less study and develop (Mintun et al. 2006; Wong et al. 2018; Mueller et al. 2020). The FDA has only approved one radiotracer to imaging tau pathology, Tauvid™ (Jie et al. 2021), which positives results come after the amyloid PET (Barthel, 2020).

The use of PET for diagnosis presents many benefits, due to its' prolonged use of almost 20 years (Zetterberg & Bendlin, 2020). (I) It is a well stablished and standardised technique, and the abnormality limits of the different biomarkers are well known (Klunk et al. 2015). (II) The high sensitivity and specificity of the three approved radiotracers (Wang et al. 2023). This means that, by using the radiotracers, AD can be accurately diagnosed, distinguishing it from other forms of dementia. (III) There are other significant advantages like the specific localization of the protein aggregates in the brain, the severity and stage of the disease and its' prognosis. For these reasons, the PET is considered a "gold standard" in clinic and is used as a reference for rest of the biomarkers and analysis methods.

Notwithstanding, PET presents some drawbacks that limit its' use. (I) In order to perform the imaging, there must be large amyloid and Tau aggregates, consequence of their accumulation throughout the years. This can lead to a misdiagnose, as during the early stages, protein aggregates are not detectable because of their size (Barthel, 2020) (II) Only a single pathology can be image, either Aβ plaques or Tau tangles (van der Flier et al. 2023). Additionally, in the case of the Tau PET, it has been proved that the Tau radiotracer has off-targets (Johnson et al. 2016; Lowe et al. 2016). (III) Regarding the socioeconomic

aspects, PET cannot be considered an accessible technique. Performing PETs is still a highly expensive technique, it requires special equipment and qualified professionals (Norberg et al. 2010; Ashton et al. 2021a; Zetterberg & Bendlin, 2021).

1.2 Biomarkers in CSF samples

CSF is the fluid that occupies the extracellular space of the brain, flowing around both hemispheres and along the spinal cord. Given that CSF is in direct contact with the central nervous system, the biochemical changes that the brain may have, are reflected in the CSF. Thus, CSF is an extraordinary source of biomarkers and, therefore, diagnostic information (Hampel, Lista & Khachaturian, 2012). The CSF is extracted through a puncture near the spinal cord and, after, the biomarkers in the fluid are detected through different immunoassays.

The parameters of the AT biomarkers in CSF are defined due to its' extensive use (Boulo et al. 2020). For the amyloid component, the 40 or 42 amino acid-long forms of Aβ (Aβ40 and Aβ42) are typically measured. Aβ40 and Aβ42 peptides are formed via the sequential cleavage of the β-amyloid precursor protein (APP) by the γ-secretase (Kang et al. 1987). Depending on the position where γ-secretase cuts, Aβ of different lengths are release (Aβ40 or Aβ42) (Porteliuset al. 2011) Aβ42 is the primary component of the Aβ plaques (Iwatsubo et al. 1994; Lewczuk et al. 2003; Lecwczuk et al. 2021), aggregating in the brain parenchyma. This accumulation results in a decrease concentration of by a 50% in CSF in AD patients (Buchhave et al. 2012; Olsson et al. 2016; Teunissen et al. 2018). Another approach is normalizing Aβ42 to Aβ total concentration, represented by Aβ40, the most abundant isoform (Lewczuk et al. 2021, Hansson et al. 2019). The value of the $Aβ_{42/40}$ ratio is reduced in patients with AD (Hansson et al. 2007; Hansson et al. 2019) and performs better than Aβ42 alone discriminating AD from healthy controls (reviewed in: Lewczuk et al. 2021). Independently, both CSF Aβ42 and $Aβ_{42/40}$ ratio are highly accurate biomarkers for AD diagnosis. For example, patients that presented mild cognition impairment (MCI), with PET-negative and CSF-positive results, the PET turned to be positive for AD 4-6 years later (Lewczuk et al. 2017; Hansson et al. 2019; Mattsson et al. 2019).

Tau can also be detected in CSF. Aggregates of hyperphosphorylated Tau accumulates intracellularly but, with the neuronal death, Tau is released to the extracellular space and, consequently, to CSF (Formichi et al. 2006; Anoop et al. 2010). Despite the lower concentration of Tau in CSF (Formichi et al. 2006), ranging between 100 to 1200 pg/mL

(Hanisch et al. 2010), it can be measured through immunoassays. Tau protein is present in CSF in two different forms: t-tau and p-tau. Regarding t-tau, the concentration is 300 times higher in AD patients than in healthy controls (Blennow,Vanmechelen & Hampel, 2001; Skillbäck et al. 2015) and this increase is detected in early stages of the disease (Parnetti et al. 2012). Although it seems an accurate biomarker, the concentration of t-tau is increased in other conditions not related to AD (Hermann et al. 2022; Papaliagkas et al. 2023). In contrast, p-tau isoforms are more accurate biomarkers than t-tau (Blennow & Zetterberg, 2018), because it changes only in patients with AD but not in other neurodegenerative diseases or dementia (Kandimalla et al. 2013). P-tau in CSF increases in patients with AD (Hampel et al. 2004; Skillbäck et al. 2015), reaching 100 times its concentration compared to healthy individuals (Kandimalla et al. 2013). In clinic, both $A\beta_{42/40}$ ratio and p-tau combined allows to determine a diagnosis with high specificity (90%) and sensitivity (93%) (Duits et al. 2014).

Thus, analysing CSF offers other advantages than PET. (I) Biomarkers in CSF come out positive before the neuroimaging techniques, making them better tools for early diagnosis. (II) To perform immunoassays is not require special equipment or specialised professionals, and it is a low-cost technique. (III) On top of that, immunoassays allow the scrutiny of more than one biomarker per sample, making the study of CSF more accessible in clinic. However, (I) the lumbar puncture is still considered a highly invasive process that must be carried out by professional with knowledge in medical procedures.

2. Present: what we are currently doing?

Brain proteins can be mobilised to blood (Ovod et al. 2017; Nakamura et al. 2018). However, this process takes place is still not perfectly understood. It is suggested that molecules are transported to blood through the glymphatic pathway (Rasmussen, Mestre & Nedergaard, 2018) and brain Aβ and Tau are highly likely to be mobilised to blood through this path. Thus, they are released from the brain cells to CSF and ultimately to blood (Fig.2) (Rasmussen, Mestre & Nedergaard, 2018). Blood has a highly complex composition, resulting in a challenging evaluation of blood biomarkers: (I) The biomarkers concentrations are extraordinarily diluted when they reach the bloodstream (Delaby, Hirtz & Lehmann, 2023). (II) The blood biomarkers analysed lacked specificity for AD, due to the peripheral expression of proteins (Delaby, Hirtz & Lehmann, 2023). This made challenging to identify which proteins were originated in the brain.

These disadvantages of blood biomarkers made initially CSF sampling more attractive. Nevertheless, the advantages that the blood biomarkers offer makes them remarkably interesting as diagnostic tools, overcoming completely the limitations of PET or CSF extraction. For instance, the minimally invasiveness, the cost-effective, and the accessibility of the assays. Consequently, there has been a great implementation in the methodologies to overcome the low specificity and sensitivity of blood AD biomarkers.

1.1 **Amyloid biomarker**

1.1.1 **Soluble amyloid precursor protein (sAPP)**

sAPPα and sAPPβ, produced through an incorrect cleavage of APP (reviewed in: Yun et al, 2020), reflect early pathophysiology of the disease (Hardy & Selkoe, 2002). However, studies that assess the levels of plasma sAPPα and sAPPβ in AD patients showed inconsistency in the results (Perneczky et al. 2013; Alexopoulos et al. 2018; Yun et al. 2020). The most recent study proved that there are no significant differences in the plasma levels of sAPPα between AD patients and healthy controls. Conversely, the same study showed that plasma sAPPβ have a higher concentration in AD patients when compared to the control group (Yun et al. 2020). Unfortunately, no further research could be found that assess the discrepancies of sAPPβ (Hanon et al. 2022) and its utility as a biomarker.

1.1.2 **Aβ40, Aβ42 and Aβ42/Aβ40 ratio**

The level of brain derived Aβ in blood are difficult to measure since the concentration decrease by 100-fold compared to CSF (Delaby, Hirtz & Lehmann, 2023). Nevertheless, the design of hypersensitive immunoassays, that increases the sensitivity and specificity, allows the measurement of Aβ in blood. The levels of plasma Aβ40, Aβ42 and Aβ42/Aβ40 ratio in AD patients are declined when compared to healthy controls, correlating with the CSF results (Janelidze et al 2016; Shin et al. 2016). The biomarker that shows the greatest decrease is Aβ42, reaching 10 pg/ml concentration, a reduction of 10 pg/ml when compared to the healthy control (Janelidze et al. 2016). The plasma Aβ42/Aβ40 ratio significantly decreases in AD patients, but not as pronounced as Aβ42 alone (Janelidze et al 2016). Remarkably, the differences between the control group and prodromal AD are rather modest when is compared to the decrease in CSF concentrations (Janelidze et al 2016; Shin et al 2016; Lee et al. 2022; Delaby, Hirtz & Lehmann, 2023). Recently, the accuracy of the plasma Aβ42/Aβ40 ratio can be increased when mass spectrometry techniques are coupled to hypersensitive immunoassays. The decreased concentration of plasma Aβ42/Aβ40 ratio with this technique can be detected during

preclinical stages of the disease (Janelidze et al. 2021; Park et al. 2022) and strongly correlate (Schindler et al. 2019; Park et al. 2022). Furthermore, mass spectrometry positive results of Aβ42/Aβ40 ratio in plasma predicted, with a range of 2 to 9 years, positive PET (Schindler et al. 2019). Nonetheless, the mass spectrometry is a highly specialized technique that required long times for sample processing, making extraordinarily difficult to use it in clinic.

2.2 Tau biomarkers

Following Aβ42 and Aβ42/Aβ40 ratio biomarkers, brain Tau protein begins to being detectable in blood. In general, AD patients present an elevated concentration of the different isoforms of Tau in plasma (Beyer et al 2023). The different forms of the protein Tau found in blood, together with Aβ42 and Aβ42/Aβ40, allows a more accurate prediction of AD, compared to when these biomarkers are used alone (Dubois et al. 2014; Chatterjee et al. 2022)

2.2.1 T-tau

The levels of the t-tau increase AD by using ultra-sensitive immunoassays, (Zetterberg et al. 2013; Chiu et al 2014; Mattson et al. 2016; Mielke et al. 2018; Fossati et al. 2019). This concentration in plasma is three times higher in AD (Chiu et al. 2014) and can be detected in early stages of the disease (Yang et al. 2018). Yet, it is unclear the value of blood t-tau as a biomarker for diagnosing AD. (I) Plasma t-tau has a poor correlation with both CSF (Zetterberg et al. 2013; Mattson et al. 2016; Fossati et al. 2019) and tau-PET (Guo et al. 2021) (II) The concentration of t-tau is not only elevated in AD, but also in other neurological conditions. For instance, vascular dementia, Creutzfeldt–Jakob's disease (Zetterberg, 2017), acute cerebrovascular events (Onatsu et al. 2020). (III) In addition, the positive results of t-tau overlap with the concentrations of healthy controls and other non-AD related dementias (Mattsson et al. 2016; Pase et al. 2019; Ashton et al 2020). This can be explained through the expression of Tau in the peripheral tissues, like the heart or the liver (Dugger et al. 2016). It is estimated that only 20% of Tau in the plasma is brain-derived (Barthélemy et al. 2020). Therefore, we conclude that measuring t-tau content is only logical in CSF but not in blood, due to the impossibility of distinguishing the protein Tau originated in the brain and other tissues.

2.2.1 P-Tau

In AD, Tau can be hiper-phosphorylated in more than 50 positions (Wesselin et al. 2020, Wegmann, Biernat & Mandelkow, 2021) and these phosphorylated isoforms can be also

detected in blood. One of the first forms to be determined was Tau phosphorylated at threonine181(p-tau181) (Tatebe et al. 2017). The concentrations of plasma p-tau181 is one to three times higher in AD patients than in their matched controls (Tatebe et al. 2017). Levels of p-tau181 correlates with both CSF p-tau181 and PET (Mielke et al. 2018; Palmqvist et al. 2019). Later, was confirmed that this changed in plasma p-tau181 is noticeable during predicting amyloid and tau PET positive results (Janelidze et al. 2020), which is around 16 years before the AD onset (Barthélemy et al. 2020).

Nonetheless, p-tau181 is not the only biomarker that is measured in blood for AD diagnosis, and some studies state that the other isoforms perform better in predicting AD (Barthélemy et al. 2020; Asthton et al. 2021a; Palmqvist et al. 2021; Milà-Alomà et al. 2022; Meyer et al. 2022; Brickman et al. 2023; Gonzalez-Ortiz et al. 2023). For example, another relevant phosphorylated form that provides information about AD in early stages is p-tau phosphorylated at threonine 231 (p-tau231) (Suarez-Calvet et al. 2020; Ashton et al. 2021b). The concentration of plasma p-tau231 in AD patients is almost the double when compared to their respective control (Ashton et al. 2021b), and this increase anticipates positive results for Aβ PET (Gonzalez-Ortiz et al. 2023, Ashton et al. 2021b). Furthermore, p-tau231 has a great sensitivity and specificity, meaning that AD is accurately distinguished from other non-AD dementias and other primary tauopathies (Ashton et al. 2021c). In comparison with p-tau181, the data suggests that p-tau231 and p-tau181 perform similarly in terms of predicting and accurately diagnose AD (Ashton et al. 2021b). Interestingly, their data shows that p-tau231 increases in subjects in preclinical stages where p-tau181 cannot be detected (Ashton et al. 2021b). Also, coupling mass spectrometry techniques to the detection immunoassays increases the accuracy in discerning AD from other types of dementia increases (Ashton et al. 2021c; Janelidze et al. 2021).

Regarding the p-tau phosphorylated at threonine 217 (p-tau217), the concentration in plasma is abnormally elevated. Plasma p-tau127 concentration is 4.4 times in AD patients than in the control group (Thijssen et al. 2021). This elevation in the concentration of plasma p-tau217 is prior to a positive result of tau PET, even 20 years before the accumulation of aggregates and the cognitive impairment appears (Barthélemy et al. 2023). This time point overcomes the increase of p-tau181, which is reported to appeared 16 years before the symptomatology manifestation (Palmqvist et al. 2020) and before than p-tau231 (Mielke et al. 2021). On top of that, a recent study comparing different

immunoassays that detects plasma p-tau217 showed that this biomarker predicts positive tau PET and is comparable to CSF positive results (Ashton et al. 2024). Thus, p-tau217 also works as a biomarker that accurately discriminates AD from other types of dementia with a high sensitivity and specificity (Palmqvist et al. 2020; Thijssen et al. 2021).

2.2.3 Brain derived Tau (BD-tau)

As stated above, the content of brain Tau in blood is difficult to detect because Tau protein is expressed ubiquitously in the organism (Barthélemy et al. 2020). Recently, the development of a new immunoassay allows the detection in blood of brain derived Tau (BD-tau) despite its diluted concentration (Gonzalez-Ortiz et al. 2023).

The approach to tackle this problem is based on the structure of Tau. Peripheral Tau contains a large exon between the exons 4 and 5, exon 4a (Georgieff et al. 1991). Instead, BD-tau forms present a direct junction between the exons 4 and 5 (Couchie et al. 1992). Thus, Gonzalez-Ortiz and colleagues (2023), designed an antibody that only binds the exon 4-5 junction of BD-tau and is unable to recognise the peripheral Tau that primarily express a 4-4a-5 region.

This study shows that the concentration of BD-tau in plasma is 9 times higher in Aβ+ groups when compared to the controls (Gonzalez-Ortiz, 2023). Contrary to plasma t-tau results, the BD-tau results showed a strong correlation with CSF measurements (Gonzalez-Ortiz, 2023). The increase concentration of BD-tau in blood is only detected in AD patients, even with mixed pathology, and not in other neurodegenerative conditions or healthy controls (Gonzalez-Ortiz, 2023). For these reasons, BD-tau has become a very promising biomarker, as it perfectly reflects the tauopathy framework with any interference of the peripheral t-tau content. However, the question that arises is why using plasma BD-tau when there are several biomarkers that allow a proper and early AD diagnosis, such as p-tau? Firstly, as Gonzalez-Ortiz (2023) points out, the known AT(N) biomarkers can be studied both in CSF and blood, but the t-tau content in CSF has no equivalent in blood. Secondly,

also believe that the purpose of the development of BD-tau is not to being used as a single biomarker, rather than using it in combination with the rest of the amyloid and p-tau biomarkers. This does not only apply to BD-tau, but also to the rest of biomarkers since the more information we have about the patient's situation, the greater chances of giving an accurate diagnosis.

3. Implementation of Zetterberg and Bendlin integrated model

We consider that is fundamental not only to know the different biomarkers that can be use but also how they develop throughout the progression of AD. In 2021, Zetterberg and Bendlin already plotted an integrated model in which the different AD-related biomarkers are represented in the different stages of the disease. We decided to upgrade this integrated model (Zetterberg and Bendlin, 2021), implementing all the information about biomarkers gathered in this review.

The first biomarker to become abnormal is Aβ, both in CSF and plasma (Fig.2). This aligns with the principle proposed in the amyloid cascade hypothesis, in which is stated that the abnormal increase of Aβ triggers the pathological events of AD (Hardy and Higgins, 1992). In the original model, Aβ42 is the only amyloid biomarker represented. In our model, we substitute plasma Aβ42 by plasma Aβ40/Aβ42 ratio, as it performs better in diagnosis than Aβ42 alone (Fig.2) (Lewczuk et al. 2021). In any case, the changes in CSF and plasma Aβ42 or Aβ40/Aβ42 stars 25 years before the symptomatology manifestation (Fig.2) (Bateman et al. 2012; Selkoe and Hardy, 2016).

The amyloid biomarker is followed closely by different forms of p-tau. According to the amyloid cascade hypothesis (Hardy and Higgins, 1992, Karran, Mercken & Strooper 2011; Karran & Strooper, 2022), the phosphorylation and released of the protein Tau is a consequence of the accumulation of extracellular Aβ. This occurs specially in p-tau217 and p-tau231, which plasma contents increase shortly after Aβ42 decreases in CSF and plasma (Fig.2) (Arslan, Zetterberg & Ashton, 2024). Out of the three p-tau isoforms, plasma p-tau217 is the first biomarker to show an abnormal concentration in AD patients. Specifically, p-tau217 levels are abnormal 20 years before AD symptomatology (Fig.2) (Barthélemy et al. 2023). Shortly after, plasma p-tau231 starts to increase, between 15-20 years of the preclinical period (Lantero-Rodriguez et al. 2021). Next, between 16-17 years before the development of AD symptoms, p-tau181 and t-tau increment their concentrations in plasma (Fig.2) (Barthélemy et al. 2020). In principle, t-tau is not a desirable biomarker for diagnosis due to its uncertain results and the poor correlation with the "gold standards" (Barthélemy et al. 2020; Frank et al. 2022). Despite this, we decided to still include t-tau in our model as is still a key biomarker that, to some extent, provides information about the state of the disease. As mentioned before, each biomarker gives essential information about the state of one specific molecule within an extraordinarily

complex process. Therefore, the more information collected, the more accurate the diagnosis will be.

Afterwards, in the model appear positive amyloid PET and positive tau PET (Fig,2). Based on the amyloid cascade hypothesis, the amyloid PET precedes tau PET (Fig.2). Additionally, both PET tests come after CSF and blood biomarkers (Fig.2), because the results are only positive when there is a large accumulation of aggregates in the brain. When this happens, the cognitive impairment is already manifesting, which difficult their use in early diagnosis. Still, our model contains these two assays, as they are currently the only technique that gives a definitely diagnosis.

The last two biomarkers reflected in the model, plasma sAPPβ and BD-tau, currently it is unclear their value as biomarkers for diagnosis. The lack of studies and the use of samples from in late stages of the disease, do not explain the state of these two biomarkers during preclinical phase (Perneczky et al. 2013; Alexopoulos et al. 2018; Yun, 2020; Gonzalez-Ortiz et al. 2023). Nonetheless, these biomarkers are strongly promising, due to their specificity to detect AD, especially BD-tau.

As a final remark, we consider that this integrated model (Fig.2) can be helpful for AD diagnosis, as it captures what and when to use each of the biomarkers along the preclinical stages of the disease.

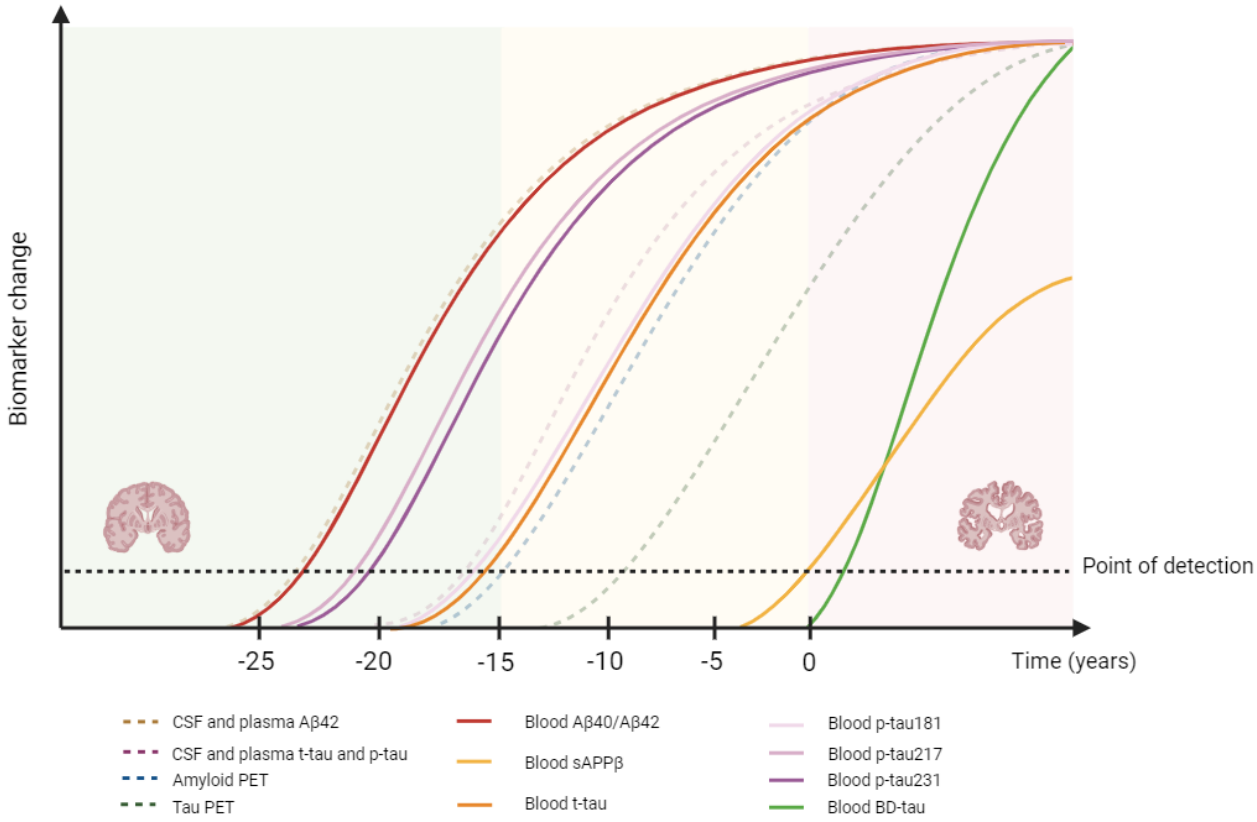

Figure 2*:* upgraded model (solid line) and comparison with Zetterberg and Bendlin (2021) model (dashed line) of the changes in the biomarkers through the AD continuum in years. The first biomarkers to present abnormal concentrations in CSF and blood are the amyloid biomarkers, Aβ42, Aβ40 and the ratio between them Aβ40/ Aβ42. As a consequence of the amyloid changes, there is an increase in the tau content, both CSF and blood. These changes are more prominent and reliable in the phosphorylated forms of the protein than in the total content, due to their direct link with AD. The first phosphorylated form that can be detected is p-tau217 in blood, closely followed by p-tau181 and p-tau231. In later scenarios of the disease, when the patient already has a cognitive impairment, amyloid PET, followed by tau PET, come out positive. Lastly, positive sAPPβ and BD-tau results appeared in the latest stages of the disease.

4. Future: What direction biomarkers have?

The development of disease-modifying therapies has shed light on patients' lives by significantly delaying the devastating AD outcomes. But by the time there is a clinical manifestation, diagnosis, and administration of a potential drug, it is late to save the severe damage brain. This is because the pathological features of AD, such as the accumulation of Aβ plaques and Tau tangles, appear several years before the symptomatology. This combined with the evidence that shows that AD treatments are more effective in the early stages of the disease (Gauthier, 2005; Atri, 2019; Rasmussen & Langerman, 2019; Mintun et al. 2021; Cummings et al 2024) makes clear that there is a need for an early AD diagnosis. For this reason, biomarkers play a pivotal role in the early AD diagnosis. Here, we collected the most used biomarkers from different origin (CSF and blood) and

techniques (imaging) for AD diagnosis. PET and CSF samples are considered gold standards in clinic. Despite this, the disadvantages like the high cost, specialisation, and invasiveness (Norberg et al. 2010; Blennow et al. 2010; Ashton et al. 2021a; Zetterberg, & Bendlin, 2021) that these procedures present make them non accessible to use as daily diagnostic tools. Conversely, the identification of biomarker in blood samples has supposed a major step forward in AD diagnosis. *A priori* blood based biomarkers fulfil all the requirements to become outstanding source for diagnostic purposes. (I) Blood biomarkers accurately predicts AD in the early stages of the disease. Several studies shown that Aβ ratios, the different p-tau forms, and, possibly, BD-tau, highly increase their concentrations in preclinical AD. Accordingly with this point, (II) blood biomarkers also present high sensitivity and specificity, being able to distinguish between AD and other neurodegenerative diseases. On top of that, (III) the cost-effective, the reduce times, the feasibility and non-invasive technique, makes blood biomarkers accessible for employ in clinic.

Although blood is a remarkable source for detecting biomarkers, and despite the great advances in this field, we still have a long way to go until they are used as a diagnostic tool on the daily basis. Blood biomarkers, in comparison with the "gold standards", still presents lower specificity, a 74% against more than an 80% (Noda et al. 2024). AD is hugely complex illness, triggered by heterogenous and multifactorial conditions (Armstrong, 2013; Badhwar et al. 2020; Aye et al. 2024). Furthermore, some neurodegenerative diseases present coexisting pathology. For instance, 60% of AD patients, during the autopsy, showed Lewy-body type synucleinopathies (Hamilton, 2000; Pollack et al. 2015; Savica et al. 2018). On the other hand, approximately the 40% of Parkinson's disease cases contain Aβ and Tau deposits (Galpern & Lang 2006; Matej,Tesar & Rusina, 2019).

Blood biomarkers still faces further obstacles regarding the sensitivity of diagnostic tests. As it happens with the specificity, blood biomarkers sensitivity decreases more than 20% when compared to PET (Noda et al. 2024). The main question that arises is why the sensitivity is so compromised? Is because these brain proteins do not reach the bloodstream or because we do not have techniques with enough sensitivity to detect them? Brain proteins move freely between the brain tissue and the CSF, but it does not happen with blood. This is because the presence of the brood-brain barrier. This structure extensively regulates the delicate CNS environment, controlling what can go inside and

outside. Pathological situations severely damage the brain-blood barrier, increasing protein's permeability to blood (reviewed in: Bellaver et al. 2023). Despite this, when brain proteins reach the bloodstream, they do it in a highly dilute levels, around pico and femto-molar concentrations (Karikari, 2022). Thus, we deduce that the short use of blood biomarkers has not allowed the development of a technology sufficiently sensitive to detect low concentrated analytes. Taking all together, this creates a great complication when it comes to give an accurate diagnosis by only using blood biomarkers, even greater when we talk about early diagnosis.

The recent use of blood biomarkers as a diagnostic tool also affects enormously the standardization and cut-off points of blood biomarkers. The only method to improve the base knowledge, as van der Flier (2023) states, is by public participation. Obtaining sufficient participants is fundamental to determine the lower and higher limits blood biomarkers (Fargo et al. 2016). Furthermore, not only we have to increase the sample size but also the diversity of the population. The vast majority of studies use middle class non-hispanic white populations (Balogun et al. 2023), and this also affects to PET and CSF samples results. Several studies reported different results between ethnic groups (Schindler et al. 2022; Hall et al. 2022). For example, the biomarkers p-tau231 and p-tau181 in plasma do not accurately predict positive amyloid PET in African American group when is compared to western populations results (Schindler et al. 2022). Hence, we believe that adding populations with different ethnicities and socio-economic backgrounds is a key factor to ultimately refining the early diagnosis, prevention, and therapy of AD patients. Currently, the scientific community is making an active and coordinated effort to tackle this problem by creating larger data bases. Institutions like CEAFA in Spain (Confederación Española de Alzheimer, [CEAFA], n.d.); or ABOARD in The Netherlands (Alzheimer Nederland, n.d.), collect information from AD patients at a national level introducing sociodemographic, health and social variables. This not only happens at national level, but also internationally. For example, the organization Alzheimer Europe, encourage the patients and general public to actively participate with researchers throughout different European projects (Alzheimer Europe, n.d.). On the same line, worldwide projects such as Davos Alzheimer's Collaborative (Davos Alzheimer's Collaborative, n.d.) or the organization Alzheimer's Disease International through their project WW-FINGERS (Alzheimer's Disease International, [ADI], n.d.), are creating global cohorts with the objective of understanding AD across a diverse

population. We consider that blood biomarkers could mean a breakthrough for stabilising global databases. As it is mentioned above, with one small blood sample multiple biomarkers can be studied in a cost-effective and in a reduce frame time. As a result, large sets of information of AD *continuum* are gathered, thing that cannot be replicated with the "gold standards". All this information ultimately helps in giving an early an accurate AD diagnosis. Moreover, these databases will help researchers to determine the root cause of AD.

Employing blood samples as a source of AD biomarkers displays more advantages. Apart from using blood biomarkers for early AD diagnosis, there are other benefits related to clinical practices (Hadjichrysanthou et al. 2020; Karikari et al. 2022). Among them, blood biomarkers enable clinicians to evaluate the patient, assessing their current state and disease prognosis. Blood biomarkers are not only helpful in the daily clinic, but also in clinical trials, allowing a fast tracking of the patient and the evolution of the disease under a treatment (Bittner, 2022). We consider that, despite their recent use, the future of blood biomarkers points towards one direction, a personalized medicine. For diseases that represent such a society challenge like AD this is fundamental, as it would improve considerably patient's life quality.

In conclusion, there is still a long process before we can use blood biomarkers in the daily basis. But it is undeniable that blood biomarkers have already set a clear way to a more accessible and accurate healthcare for a disease that increases in the number of patients every year. We conclude that enhancing the research in molecular AD prevention, diagnosis, and treatment is crucial if we, as a society, want to turn AD in the near future into a curable disease.

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