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Phospholipid biomarkers in the diagnosis of patients with Alzheimer's disease

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ABSTRACT: Alzheimer's disease is a neurodegenerative disease characterized by an accumulation of amyloid beta peptide and hyperphosphorylation of Tau protein, as well as alterations in lipids that are important components of cell membranes. However, the mechanism of phospholipids in AD is not yet fully understood. This mini-review aims to explore the role of phospholipid biomarkers in the diagnosis, prognosis, and progression of the disease. A search was performed in several databases, including PubMed, PubMed Central, and ScienceDirect, with keywords such as "phospholipid biomarkers," "Alzheimer," and "non-sporadic diagnosis." A total of 30 articles were found, in which we discovered that phospholipid species such as ceramides, sphingomyelins, phosphatidylcholines, lysophosphatidylcholines, ethanolamine plasmalogens, phosphatidylethanolamines, and 2-aminoethyl dihydrogen phosphate were altered, showing that plasma lipids can be used as biomarkers for the diagnosis of AD, as well as to predict the prognosis and classify the severity of the disease. Nevertheless, although the findings are promising, further clinical validation through larger, more extensive studies is still required to consolidate their diagnostic and prognostic applications.

Keywords: Biomarkers; Alzheimer's disease; Diagnosis; Phospholipids.

1.0 INTRODUCTION

Alzheimer's disease is characterized by a progressive decline in memory associated with neuronal degeneration, morphological alterations, and metabolic disturbances involving proteins, lipids, and other metabolites, which may either decrease or increase across different regions of the body—particularly in the brain—ultimately leading to the manifestation of clinical symptoms (Han, 2005). This pathology typically evolves gradually and compromises higher cognitive functions, including thinking, learning, speech, and the ability to perform daily activities. The most commonly recognized risk factors include advanced age, dysregulated lipid metabolism, and genetic predispositions such as the ε4 allele of apolipoprotein E (Ceccom et al., 2014; Dorninger et al., 2018).

Neuropathologically, AD is characterized by the accumulation of amyloid deposits in the cerebral cortex, the presence of neurofibrillary tangles, and widespread neuronal death (Ceccom et al., 2014; Han, 2005). Consequently, the biomarkers most frequently employed for diagnostic purposes include phosphorylated tau protein (P-tau) (Kosicek & Hecimovic, 2013), total tau, neurofilament light chain (NFL), and beta-amyloid peptide, all of which contribute to an approximate diagnosis of the disease (Banack et al., 2022). In general terms, a biomarker is defined as a biological substance that enables the detection of biochemical alterations associated with a disease, identifies characteristics that determine risk and progression, and distinguishes the presence of pathological conditions. Accordingly, alterations in brain lipid profiles can also be reflected in blood-based biomarkers, representing a promising avenue for the early detection and monitoring of AD (Agarwal & Khan, 2020; Kim et al., 2017).

In living organisms, lipids fulfill a wide range of essential biological functions. They provide structural integrity to cells and organelles through the formation of lipid bilayers, generate chemical and physiological environments that facilitate protein interactions and activities, act as precursors for diverse signaling molecules, and serve as reservoirs of metabolic energy. In many regions of the human body, lipid levels are subject to strict regulation. The central nervous system (CNS), which contains the second-highest concentration of lipids in the body, is particularly dependent on balanced lipid metabolism for its proper function (Kosicek et al., 2010). The critical roles of lipids are especially evident when the cerebral lipid alterations occur, as these have been associated with a range of neurological disorders—including Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis—where disruptions have been reported particularly in sphingolipids and phospholipids, two fundamental subclasses of membrane lipids (Czubowicz et al., 2019; Han, 2005). Notably, thousands of molecular lipid species exist within cells, interacting both within specific subcellular compartments and across different regions of the lipid bilayer. Among these, phospholipids represent the predominant class in most mammalian cells; they are composed of a phosphodiester head group linked to the sn-3 position of a glycerol backbone and account for approximately 60% of total cellular lipids (Han, 2005).

It could be expected that these biological molecules, phospholipids, indicate the onset of certain neurodegenerative diseases, including Alzheimer's disease, since they are structural components of cell membranes and could be used as earlier biomarkers in the course of the disease. Phospholipids are the most abundant lipids in neuronal membranes, forming lipid bilayers in which their polar head groups align with aqueous interfaces while their hydrophobic tails cluster inward. This organization generates the semi-permeable barriers of cellular and subcellular membranes. Their dynamic remodeling enables rapid changes in membrane shape and function, which are essential for synaptic transmission and structural synaptic integrity. Additionally, phospholipids play a critical role in regulating enzymes, membrane proteins, and ion channels, both intracellularly and at the cell Surface. Given that the brain is one of the organs with the highest lipid content, alterations in phospholipid metabolite levels have been correlated with neuropathological disease features and measures of cognitive decline. Disruptions in Specific phospholipid metabolic pathways suggest a potential mechanism for increased amyloid deposition in Alzheimer's disease, secondary to membrane alteration. They may help explain the association between the apoE genotype and elevated risk of Alzheimer's disease (Pettegrew et al., 2001).

Certain groups of phospholipids are more commonly studied, such as sphingolipids (Agarwal & Khan, 2020; Czubowicz et al., 2019; Su et al., 2021), phosphoglycerols, phosphatidylethanolamines (PE) (Dakterzada et al., 2022; Gaitán et al., 2021; Khan et al., 2022), ethanolamine plasmalogens (PLsEtn) (Dakterzada et al., 2022; González-Domínguez et al., 2014; Wood et al., 2015), 2-aminoethyl dihydrogen phosphate (Banack et al., 2022), phosphatidylcholines (PC) (Dakterzada et al., 2022; Gaitán et al., 2021; Su et al., 2021), lysophosphatidylcholines (lysoPC) (Dakterzada et al., 2022; Khan et al., 2022), as well as ceramides (Czubowicz et al., 2019; Kosicek & Hecimovic, 2013; Wong et al., 2017), which are highly relevant in the prognosis of the disease. Therefore, the purpose of this review is to gather information about the scientific evidence regarding the potential use of phospholipids as biomarkers for the early diagnosis of Alzheimer's disease (AD).

2.0 MATERIALS AND METHOD

This exploratory Review followed the PRISMA guidelines. An exclusive search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/) between November 2023 and January 2024. The MeSH (Medical Subject Headings) terms 'biomarkers' phospholipids',

Alzheimer', diagnosis' sporadic' were combined to create the search matrix: (biomarkers) AND (phospholipids) AND (Alzheimer) AND (diagnosis) NOT (sporadic). A total of 76 articles were retrieved from the database. Article selection was conducted by reviewing titles and abstracts and retaining those aligned with the research objective. Subsequently, the most relevant studies were identified by utilizing inclusion and exclusion criteria.

Inclusion Criteria: The collection of studies included patients with an early diagnosis of familial Alzheimer's disease, family members of patients diagnosed with Alzheimer's disease who tested positive for the mutation, systematic reviews, and lipidomic studies.

Exclusion Criteria: The exclusion criteria were as follows: type of document (letters to the editor), limited access to the abstract, other pathologies (Parkinson's, diabetes, brain tumors, and migraines), other dementias (frontotemporal), in vitro studies or animal model experiments, and biomarkers other than lipids (proteomics).

The study selection process is summarized in the flowchart in **Figure 1**.

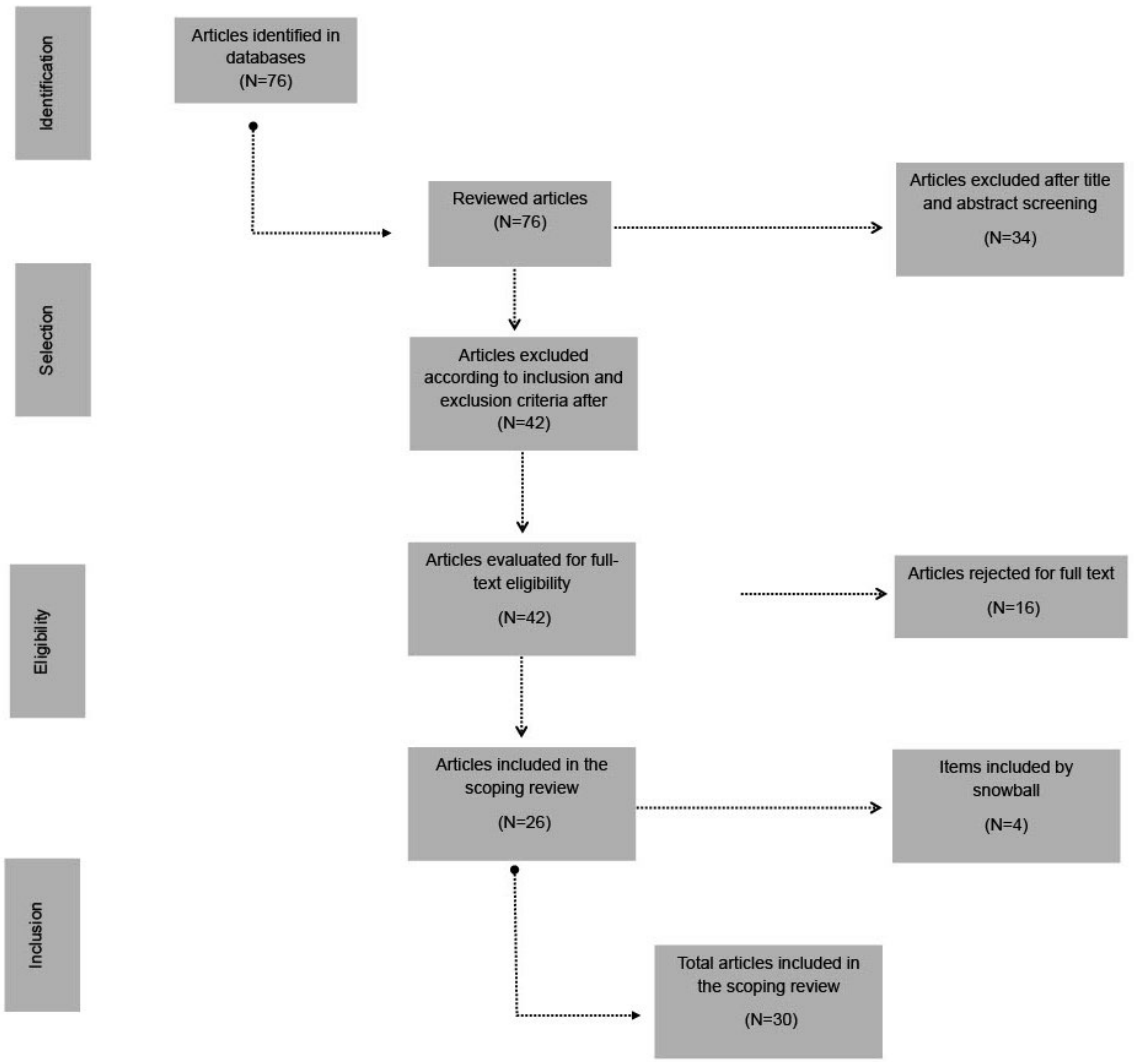

Figure 1. Information selection flowchart.

A total of 76 studies were identified from the databases. Filters were applied according to the inclusion criteria (human studies with mild cognitive impairment, patients with prodromal Alzheimer's disease, observational studies, systematic reviews, and non-experimental lipidomic studies in animals), and the studies were screened and reduced to 42. After further filtering, 26 relevant studies were retained (1–26).

These include 21 clinical trial articles, 4 narrative review articles, 1 systematic review, and 1 Mendelian randomization study. In terms of timeline, one article was published in 2003 (Han et al., 2003), one article in 2009 (McIntyre et al., 2009), one article in 2010 (Mielke et al., 2010), two articles in 2011 (Mielke et al., 2011; Orešič et al., 2011), one article in 2013 (Kosicek & Hecimovic, 2013), five articles in 2014 (Ceccom et al., 2014; Cui et al., 2014; González-Domínguez et al., 2014; Mapstone et al., 2014; Wurtman, 2015), two articles in 2015 (Koal et al., 2015; Wood et al., 2015), two articles in 2017 (Kim et al., 2017; Wong et al., 2017), one article in 2018 (Dorninger et al., 2018), one article in 2019 (Czubowicz et al., 2019), three articles in 2020 (Agarwal & Khan, 2020; Chen et al., 2020; Kling et al., 2020), three articles in 2021 (Gaitán et al., 2021; Lord et al., 2021; Su et al., 2021), and three articles in 2022 (Banack et al., 2022; Dakterzada et al., 2022; Khan et al., 2022). No articles were found for the years 2023 and 2024.

Additionally, a total of four articles were identified through snowball sampling, including three systematic reviews and one clinical trial. Regarding their distribution by year of publication: one article was published in 2001 (10), one in 2005 (1), one in 2010 (8), and one in 2013 (9). The main findings from the 30 selected articles are summarized in **Supplementary Table 1** and illustrated in **Figure 1**.

3.0 DISCUSSIONS

3.1 Ceramides and sphingomyelin in the early stage of Alzheimer's disease

Ceramides are key metabolites of sphingomyelin (SM), functioning both as precursors in SM synthesis and as products generated through SM hydrolysis. Beyond their structural role, ceramides act as bioactive second messengers that regulate critical cellular processes, including differentiation, proliferation, and apoptosis, by activating signaling cascades and promoting free radical generation (Mielke et al., 2010). Importantly, ceramides have also been implicated in Alzheimer's disease pathology by stimulating the production of beta-amyloid peptide. This occurs through the extension of the half-life of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), which catalyzes the processing of amyloid precursor protein into beta-amyloid peptide, thereby reinforcing a self-perpetuating and deleterious cycle (Wong et al., 2017). Given the biochemical role of ceramides in cell signaling and in the production of the beta-amyloid peptide, several clinical studies have evaluated their relationship with cognitive impairment and the risk of Alzheimer's disease. In 2017, Wong reported that baseline ceramides C22:0 and C24:0 predicted memory impairment and reduced hippocampal volume in patients with mild cognitive impairment.

Additionally, high baseline levels of ceramides C16:0 and C24:0 are associated with an increased risk of Alzheimer's, like patients with low serum ceramide levels (Wong et al., 2017). These insights show how specific types of ceramides could be early indicators of cognitive and structural changes in the brain. Similarly, in 2010, Mielke and other authors found that ceramides are often associated with memory impairment in delayed recall and that high levels predicted incident cognitive decline over time (Mielke et al., 2010). As a result, it can be inferred that during early cognitive decline, before the clinical onset of Alzheimer's disease, ceramide levels are likely to increase, which could be associated with an increased risk of neurodegeneration. In the same way, Kosicek & Hecimovic (2013) report that ceramide levels are elevated in mild cognitive impairment, which may be due to positive feedback in ceramide metabolism genes and negative feedback in glycosphingolipid synthesis genes. In summary, elevated ceramide levels reflect an alteration in sphingolipid metabolism. This process is triggered when the beta-amyloid peptide activates acid, alkaline, and neutral sphingomyelinases, which degrade sphingomyelin and promote its accumulation. This mechanism, in turn, enhances the production of beta-amyloid peptide.

Clinical and laboratory studies suggest that alterations in sphingomyelins (SM) and the ceramide/SM ratio may play a significant role in the pathophysiology of Alzheimer's disease (AD), particularly in the formation of beta-amyloid peptide, the development of amyloid plaques, and the progression of neurodegeneration. Evidence further indicates that sphingolipid levels in the brain tissue of AD patients are markedly altered when compared with cognitively normal controls (Mielke et al., 2010). SM are ubiquitous components of cellular membranes, with particularly high concentrations in the central nervous system, where they are indispensable for the formation of membrane microdomains, or lipid rafts. These specialized structures provide a platform for essential processes such as signal transduction, membrane trafficking, and protein sorting. Given their close association with apoptotic pathways, sphingomyelins and related sphingolipid alterations may represent valuable indicators of preclinical neurodegeneration (Mielke et al., 2010; 2011). In this context, clinical research has documented specific alterations in sphingomyelin levels in Alzheimer's

patients compared to controls. In a cross-sectional study, it was found that sphingomyelin species were reduced in AD compared to controls, while ceramides C16 and C21 were increased in AD. Consistently, Mielke et al. (2011) mention that alongside elevated ceramide levels, there is a reduction in sphingomyelins during the clinical stage of AD. Czubowicz et al. (2019) state that in AD, a proportion of stress factors contribute to increased ceramide production, indicating further alteration in sphingomyelin metabolism. Coinciding with these observations, it is important to highlight the activation of neutral sphingomyelinase, leading to elevated ceramide levels, which matches with an increase in ceramides and a reduction in sphingomyelin that may be considered biological markers of the onset of cognitive impairment and subsequent dementia (see **Figure 2**).

3.2 Phosphatidylcholines and lysophosphatidylcholines decrease in the preclinical stage of Alzheimer's disease

Phosphatidylcholines (PC) are fundamental components of cellular membranes, including synaptic membranes, and are also present in blood plasma. PC metabolism occurs primarily through deacylation, a process that sequentially releases its two fatty acids, initially generating lysophosphatidylcholine and subsequently glycerophosphocholine (Wurtman, 2015). Lysophosphatidylcholine is produced through the hydrolysis of PC mediated by phospholipase A2 and participates in the deacylation-reacylation cycle. Importantly, this metabolite plays a key role in maintaining the composition and stability of glycerophospholipids within neuronal membranes (Cui et al., 2014).

In a landmark study, Mapstone et al. (2014) conducted a 5-year longitudinal investigation involving 525 cognitively healthy participants aged 70 and older. The cohort was divided into three groups: 1) individuals who later developed mild cognitive impairment (MCI)/AD) 2) Converters —participants who transitioned from normal cognition to MCI or AD during the study period and 3) cognitively healthy controls. This design enabled the identification of phospholipid alterations associated with the prodromal stages of AD, highlighting the potential of PC and its metabolites as early biomarkers of cognitive decline. They conducted an analysis that revealed phospholipids as potent discriminators among cognitively normal groups, amnestic MCI, and early Alzheimer's disease. This analysis showed significantly low plasma levels of PC in participants before conversion, who would later develop Alzheimer's disease or amnestic MCI. The reports by Mapstone et al. (2014) are significant in that they link phosphatidylcholine metabolism to cognitive decline. The decrease in plasma PC in subjects who subsequently developed mild cognitive impairment or Alzheimer's disease suggests an early variation in the deacylation-reacylation pathway. Under normal conditions, this process ensures the balance of phospholipids in the neuronal membrane. Low PC levels could reflect a disruption in this cycle, compromising synaptic membrane homeostasis and, consequently, neuronal transmission. Thus, the changes observed in the lipid profile not only act as early biomarkers but also offer a pathophysiological link to disease. In line with the results described, several studies have reported significant alterations in phosphatidylcholine (PC) metabolism in Alzheimer's disease (AD). Plasma analyses have demonstrated decreased levels of PC and reduced lysophosphatidylcholine-to-PC ratios, alongside increased concentrations of PC metabolites in cerebrospinal fluid (CSF) of AD patients (Mapstone et al., 2014).

In a complementary study, Cui et al. (2014) analyzed serum and urine samples from 46 individuals diagnosed with AD and 37 cognitively healthy controls, finding markedly reduced levels of lysophosphatidylcholine (18:0), lysophosphatidylcholine (20:3), and lysophosphatidylcholine (18:2). These findings suggest a disruption in lipid metabolism associated with AD. Furthermore, authors have reported that phospholipase A2 activity is significantly reduced in the parietal and temporal cortices of AD patients, a mechanism that could contribute to diminished serum lysophosphatidylcholine levels. Collectively, these alterations, which could lead to low serum lysophosphatidylcholine levels in AD, may serve as early biomarkers of the disease (Cui et al., 2014).

In a study performed by Wong et al. (2017), specific alterations in phospholipids were investigated, revealing that three PC—PC 16:0/20:5, PC 16:0/22:6, and PC 18:0/22:6—were significantly reduced in patients with AD and MCI compared to cognitively healthy controls. This finding was consistent across both, an initial screening cohort of 35 participants and a subsequent validation phase involving a larger sample of 141 patients. Notably, reductions in these lipids were also correlated with poorer memory performance in non-demented older adults, suggesting that altered phospholipid metabolism may represent a shared mechanism underlying both AD pathology and age-related cognitive changes. Building on these findings, a

follow-up lipidomics analysis identified additional PC and lysophosphatidylcholine species that differentiated AD and MCI patients from controls. Among these, the ratio of phosphatidylcholine 34:4 to lysophosphatidylcholine C18:2 demonstrated strong diagnostic potential, distinguishing controls from individuals with AD and MCI with an accuracy ranging from 82 to 85%.

As previously stated, PC and lysophosphatidylcholines are reduced in the brains of individuals with MCI and patients with AD. The data collected suggest that reductions in these molecules could represent changes in lipid metabolism in both healthy older adults and those who are beginning to develop Alzheimer's disease, correlating with memory performance in both groups and suggesting that monitoring PC and lysophosphatidylcholines could offer valuable information on early molecular processes and serve as potential tools for identifying and monitoring the pathology (see **Figure 2**).

3.3 Ethanolamine plasmalogens and phosphatidylethanolamines as biomarkers in the progression of the disease

In Alzheimer's disease, a deficit of ethanolamine plasmalogens (PlsEtn) and phosphatidylethanolamines (PE) has been reported. Plasmalogens are integral membrane components that appear to play important roles in the pathophysiology of Alzheimer's disease, including vesicular fusion required for the release of synaptic neurotransmitters, modulation of membrane fluidity and microdomain dynamics, membrane antioxidant functions, and neuroprotection (Kling et al., 2020). PlsEtn can exert reciprocal effects with cholesterol on membrane fluidity and lipid microdomain composition, promoting the degradation of amyloid precursor protein (APP) by alpha-secretase into non-amyloidogenic peptide products (Kling et al., 2020). This enhancement of APP breakdown mediated by alpha-secretase can reduce the production of beta-secretase-derived peptides and, consequently, the formation of amyloid plaques characteristic of the neuropathology of Alzheimer's disease. The synthesis of endogenous plasmalogen occurs in peroxisomes, particularly in the liver (Kling et al., 2020). Given the above, it can be inferred that dramatic decreases in brain PlsEtn lead to subsequent demonstrations of peroxisomal dysfunction. To illustrate, in the brains of individuals with AD, a reduction in plasmalogens was found in those with dementia. At the same time, no decrease was observed in individuals with MCI, supporting earlier reports of normal PlsEtn levels in people with MCI (Wood et al., 2015).

In a study conducted by Wood et al. (2015), PlsEtn, particularly those with polyunsaturated fats (PlsEtn 36:4, PlsEtn 38:4, PlsEtn 38:6, PlsEtn 40:4, PlsEtn 40:6), were found to be decreased in the gray matter of individuals with dementia. Cerebrospinal fluid plasmalogens were very low and extremely variable. Recent evidence suggests that PlsEtn deficiency does not typically manifest in the early stages of AD. However, in more advanced phases, the reduction of these molecules may contribute to neural deterioration. When PlsEtn levels decline, synaptic communication becomes impaired, which in turn disrupts memory, attention, and other cognitive functions commonly compromised during MCI (Wood et al., 2015). Among the biomarkers studied, PE have been identified as particularly relevant indicators of this pathological process. PE are glycerophospholipids that serve as structural components of cellular membranes, regulating membrane fluidity, participating in cell signaling, and playing a fundamental role in synaptic transmission. (Wong et al., 2017). Polyunsaturated PE (PE 36:4, PE 38:4, PE 38:6, PE 40:4) were decreased in the gray matter of individuals with mild cognitive impairment (MCI), as well as in those with dementia (Wood et al., 2015). It has also been reported that the development of dementia is partially characterized by a specific compensatory factor, namely the failure of peroxisomal mechanisms necessary to sustain plasmalogen biosynthesis relative to the corresponding phosphatidylethanolamines, which do not require peroxisomes for biosynthesis (Kling et al., 2020). The increased remodeling by phospholipases and degradation through lysoplasmalogenases and oxidative pathways could contribute to the relative reductions in plasmalogen levels (Kling et al., 2020).

Taken together, alterations in these membrane phospholipids highlight the progression of AD. Research has shown that PlsEtn tend to decrease primarily during the advanced stages of the disorder, reflecting progressive peroxisomal dysfunction and the accumulation of synaptic damage. In contrast, polyunsaturated PE exhibit reductions as early as the MCI stage, suggesting that these lipids are more sensitive to early changes in neuronal communication. Consequently, both PlsEtn and PE emerge as essential components for preserving synaptic function and the integrity of neuronal networks, with the latter potentially serving as early biomarkers of AD progression (see **Figure 2**).

3.4 2-aminoethyl dihydrogen phosphate decreased in Alzheimer's disease

The molecule commonly referred to in earlier literature by various names—including O-phosphorylethanolamine, calamine phosphoric acid, ethanolamine O-phosphate 2, O-phosphoethanolamine, O-phosphocolamine, and colamine phosphoric acid—is formerly designated by the IUPAC name 2-aminoethyl dihydrogen phosphate (Banack et al., 2022). This compound plays a critical role in the structure and function of cell membranes, serving as a precursor in the biosynthesis of both phosphatidylethanolamine and phosphatidylcholine. In mammals, it is also essential for the formation of glycosylphosphatidylinositol (GPI)-anchored proteins in mammals, which tether other proteins to the plasma membrane. GPI may play a role in cell communication, cell signaling, signal transduction, and the transport of lipid rafts (Banack et al., 2022).

Given the importance of these biological functions, alterations in the levels of 2-aminoethyl dihydrogen phosphate may have profound consequences for neuronal integrity. Indeed, Banack et al. (2022) reported that brain concentrations of this metabolite were significantly lower in patients with Alzheimer's disease compared to cognitively healthy controls. Specifically, reductions were observed in the temporal cortex (64%, Brodmann area 21), frontal cortex (48%, Brodmann area 9), and hippocampus (40%). By contrast, no significant differences were found in the parietal region (Brodmann areas 3–12) or occipital cortices (Brodmann area 17) (Banack et al., 2022). Analyses suggest that the reduction of 2-aminoethyl dihydrogen phosphate does not occur uniformly across the brain in patients with AD. Instead, this decline appears to be concentrated in regions associated with key cognitive functions (see **Figure 2**).

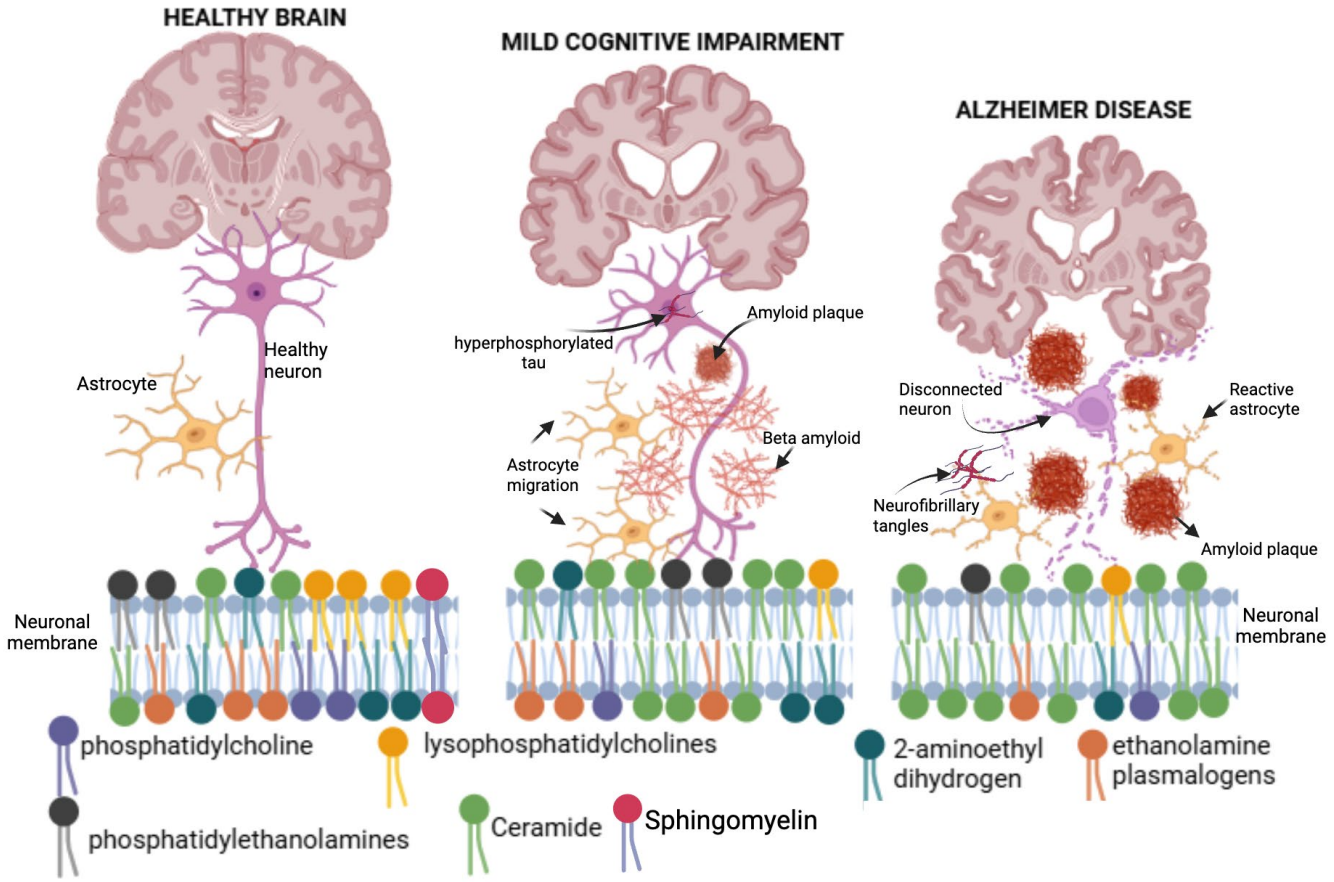

Figure 2. Alterations in Membrane Phospholipid Composition Throughout the Progression of Alzheimer's Disease. In a healthy brain, the levels of sphingomyelins, phosphatidylcholines, phosphatidylethanolamines, ethanolamine plasmalogens, and 2-aminoethyl dihydrogen phosphate remain balanced. In mild cognitive impairment (MCI), an increase in ceramides is observed due to sphingomyelin degradation, accompanied by a decrease in phosphatidylcholines and lysophosphatidylcholines. In Alzheimer's disease (AD), changes in membrane lipid composition become more pronounced, with a significant increase in ceramides and a reduction in 2-aminoethyl dihydrogen phosphate, phosphatidylcholines, phosphatidylethanolamines, ethanolamine plasmalogens, and phosphatidylethanolamines, all of which contribute to neurodegeneration. Created in BioRender. Gutierrez, J. (2026) https://BioRender.com/u8u8tu4

3.5 Biological interrelationship of phospholipids in Alzheimer's disease

The interaction among ceramides, sphingomyelin, phosphatidylcholine, and phosphatidylethanolamine in AD primarily occurs through shared metabolic pathways and complementary functions related to oxidative stress in neuronal membranes (Dakterzada et al., 2022; Gaitán et al., 2021; Su et al., 2021). Sphingomyelin is converted into ceramides by sphingomyelinases, a process that is upregulated in AD, leading to elevated ceramide levels that promote neuronal apoptosis and inflammation (Czubowicz et al., 2019; Kosicek & Hecimovic, 2013; Wong et al., 2017). Phosphatidylcholine, in turn, donates the phosphocholine group to ceramides for the synthesis of sphingomyelin via sphingomyelin synthase (SMS). In Alzheimer's disease, the reduction of phosphatidylcholine limits sphingomyelin synthesis, thereby compromising membrane stability.

In addition, ethanolamine plasmalogens constitute a specific class of phospholipids with unique antioxidant properties. Their decline in AD renders neurons more vulnerable to ceramide-induced damage (Dakterzada et al., 2022; González-Domínguez et al., 2014; Wood et al., 2015). The imbalance and cross-regulation of these lipids consequently disrupt neuronal membrane integrity and impair the formation of lipid rafts, which are critical for cellular signaling. This cascade contributes to altered processing of proteins such as amyloid precursor protein (APP) and tau, both of which are central to Alzheimer's pathology. Ultimately, these molecular disturbances converge to drive progressive cognitive decline, which, when sustained over time, culminates in dementia.

3.6 Phospholipids as potential therapeutic targets in MCI and Alzheimer's disease

In future scenarios, certain phospholipid biomarkers, as discussed throughout this document, may be used to develop new therapeutic interventions, given their potential to be modulated in the early stages of Alzheimer's disease, with MCI representing a potential window for treatment. It has also been documented that, in addition to serving as structural components of various cell types, specifically neuronal membranes, in this context, these biomarkers participate in neuronal homeostasis and the regulation of enzymes involved in the cleavage of APP (Bennet et al., 2013). This regulation promotes non-amyloidogenic pathways and reduces the concentration of beta-amyloid peptide, whose extracellular accumulation can interfere with cellular signaling.

From this perspective, an initial approach to managing and slowing the progression of AD could involve the use of phospholipid biomarkers, as regulating these lipids may help preserve neuronal integrity and improve synaptic function. Considering the differential behavior of phospholipid biomarkers during the progression of Alzheimer's disease, their use as clinical interventions in various stages of the pathology becomes plausible. Biomarkers such as sphingomyelin, phosphatidylcholine, lysophosphatidylcholine, and 2-aminoethyl dihydrogen phosphate have shown reduced level in individuals with mild cognitive impairment (see **Figure 3**). During this phase, their regulation presents an opportunity to maintain neuronal stability and enhance synaptic transmission, which could be critical in early therapeutic strategies. Moreover, other biomarkers—such as ethanolamine plasmalogens and phosphatidylethanolamine—may offer a therapeutic alternative to slow neuronal degeneration and preserve cognitive function in more advanced stages of the disease. Their role in neuroprotection suggests that regulating these molecules may Help attenuate neuronal damage, particularly as their alterations tend to occur during the later phases of AD (see **Figure 3**).

Although AD can be diagnosed in specialized clinics with over 95% accuracy through a combination of tools—including clinical history, neuropsychological testing (NINCDS-ADRDA criteria, and neuroimaging—the greatest challenge for clinicians and for the implementation of new therapies lies in accurately identifying patients with prodromal AD and/or individuals with MCI who will progress to AD. Alterations in brain phospholipids, as well as in biological fluids such as cerebrospinal fluid (CSF) and blood, have attracted clinical interest because of their potential value for early diagnosis and disease monitoring. These lipid changes may serve as promising biomarkers for the detection and follow-up of AD in its initial stages. However, the phospholipid alterations reported to date in CSF and blood have not demonstrated sufficient specificity or sensitivity to be considered stand-alone diagnostic biomarkers. Instead, a combined assessment of different phospholipid levels in CSF and/or blood may contribute to achieving a more accurate and earlier diagnosis of AD.

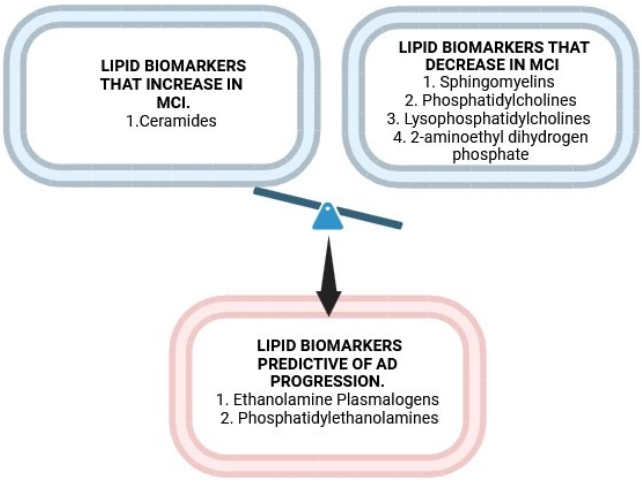

Figure 3. Altered Phospholipid Biomarkers in Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). In mild cognitive impairment, an increase in ceramides is observed, while several phospholipid biomarkers decrease, including sphingomyelin, phosphatidylcholine, lysophosphatidylcholine, and 2-aminoethyl dihydrogen phosphate. In the progression from MCI to AD, ethanolamine plasmalogens (PlsEtn) and phosphatidylethanolamines (PE) can be identified as the best predictive biomarkers, since PlsEtn show significant reductions in individuals with dementia, indicating that their gradual deficit marks the transition to the more advanced phase, while PEs decrease in both MCI and Alzheimer's disease, evidencing early and consistent alterations in the neuronal membrane that persist as the disease progresses.

4.0 CONCLUSIONS

The brain is particularly enriched in phospholipids, which are fundamental structural components of cellular membranes. Variations in the concentrations of these biomolecules, however, have been shown to contribute to the pathophysiology of AD (**Figure 3**). Key phospholipids implicated in this context include ceramides, sphingomyelins, phosphatidylcholines, lysophosphatidylcholines, ethanolamine plasmalogens, phosphatidylethanolamines, and 2-aminoethyl dihydrogen phosphate. Dysregulation of the enzymes responsible for their biosynthesis and degradation results in significant alterations in their levels, many of which have been detected in both MCI and AD.

Multiple studies report elevated concentrations of ceramides coupled with reduced levels of sphingomyelins, phosphatidylcholines, and lysophosphatidylcholines in individuals with MCI who subsequently developed dementia, suggesting that their potential utility as biomarkers for assessing the risk of AD. Conversely, other investigations have demonstrated increased levels of these biomarkers, particularly lysophosphatidylcholines, yielding results that appear contradictory. Equally relevant are phosphatidylethanolamines and ethanolamine plasmalogens, which consistently exhibit decreased concentrations in individuals already diagnosed with AD, positioning them as candidate biomarkers associated with disease progression rather than early detection.

Supplementary Materials: Table S1: Summary of the results of the articles that make up the scoping review

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Conflicts of Interest: The authors declare no conflict of interest.

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