Universidade de Lisboa

Faculdade de Farmácia

Lipid Alterations in Neurodegenerative Diseases: From Pathogenesis to Potential Therapies

Focus on Alzheimer's Disease

Raquel Marques Nobre

Monografia orientada pela Professora Doutora Liana C Silva,
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Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Existe uma relação complexa entre o metabolismo lipídico e a doença de Alzheimer, uma doença neurodegenerativa e a principal causa de demência. À medida que a população mundial envelhece, a incidência da doença de Alzheimer continua a aumentar, apresentando desafios significativos aos sistemas de saúde no mundo inteiro, representando um fardo social e de saúde significativo. Este trabalho explora a patogénese da doença de Alzheimer, enfatizando fatores genéticos e ambientais, como dieta e metabolismo lipídico.

Alterações lipídicas específicas, incluindo alterações nos glicerofosfolipídios, esfingolipídios e níveis de colesterol, são consistentemente observadas em pacientes com doença de Alzheimer. Estas alterações lipídicas contribuem para a formação de placas amiloides e nós neurofibrilares, exacerbando o dano neuronal e o declínio cognitivo. Fatores genéticos, particularmente a presença do alelo ApoE4, influenciam significativamente o metabolismo lipídico e estão associados a um risco aumentado de desenvolvimento da Doença de Alzheimer. O alelo ApoE4 afeta o metabolismo dos esfingolipídios e do colesterol, levando à acumulação de lipídios no cérebro e promovendo a patogénese da doença de Alzheimer. Fatores ambientais, como a dieta, também desempenham um papel, com elevada ingestão de gordura saturada e baixo teor ácidos gordos polinsaturados (PUFAs), contribuindo para a desregulação lipídica e aumentando o risco de Alzheimer.

Apesar do potencial promissor das estratégias terapêuticas baseadas em lipídios, desafios como a complexidade das interações lipídicas no cérebro, a passagem através da barreira hematoencefálica e a variabilidade individual na resposta ao tratamento devem ser abordados. No entanto, alguns estudos pré-clínicos e clínicos a decorrer, estão a explorar novas estratégias como modificações dietéticas, melhoria do transporte lipídico e regulação do metabolismo do colesterol, usando tanto moléculas pré-existentes como moléculas recentemente desenvolvidas. Estes estudos apresentam oportunidades e desafios na passagem dos resultados das pesquisas para a aplicação clínica.

No entanto, ainda há necessidade de uma compreensão mais profunda do metabolismo lipídico na Doença de Alzheimer, uma vez que a sua prevalência mundial continua a aumentar. Um avanço continuo neste campo de pesquisa poderá oferecer novos potenciais caminhos terapêuticos, aumentando a qualidade de vida e influenciando a progressão da doença em pacientes futuros.

Palavras-chave: doença de Alzheimer, metabolismo lipídico, ApoE4, Colesterol, Proteína Tau, Amiloide-β

Abstract

There is an intricate relationship between lipid metabolism and Alzheimer's disease, a prevalent neurodegenerative disorder and the leading cause of dementia. As the global population ages, the incidence of Alzheimer’s disease continues to rise, presenting significant challenges to health systems worldwide and posing a significant societal and healthcare burden. This work explores the pathogenesis of Alzheimer’s Disease, emphasizing genetic and environmental factors such as genetics, diet, and lipid metabolism.

Specific lipid alterations, including changes in glycerophospholipids, sphingolipids, and cholesterol levels, are consistently observed in Alzheimer’s Disease patients. These lipid changes contribute to the formation of amyloid plaques and neurofibrillary tangles, exacerbating neuronal damage and cognitive decline. Genetic factors, particularly the presence of the ApoE4 allele, significantly influence lipid metabolism and are associated with an increased risk of developing Alzheimer’s Disease. The ApoE4 allele affects sphingolipid and cholesterol metabolism, leading to lipid accumulation in the brain and promoting Alzheimer’s Disease pathogenesis. Environmental factors such as diet also play a role, with high saturated fat intake and low omega-3 polyunsaturated fatty acids (PUFAs) contributing to lipid dysregulation and increased Alzheimer's risk.

Despite the promising potential of lipid-based therapeutic strategies, challenges such as the complexity of lipid interactions in the brain, delivery across the blood-brain barrier, and individual variability in treatment response must be addressed. Nevertheless, ongoing preclinical and clinical studies are exploring novel strategies such as dietary modifications, enhancement of lipid transport, and regulation of cholesterol metabolism, using both existent and newly developed molecules. These efforts present opportunities and challenges in translating research findings into clinical applications.

However, there is still a need for a deeper understanding of lipid metabolism in Alzheimer’s Disease, given its increasing global prevalence. Continuous advancements in this field of research might offer new insights into potential therapeutic avenues, ultimately improving quality of life and influence disease progression for future patients.

Keywords: Alzheimer’s disease, lipid metabolism, ApoE4, Cholesterol, Tau Protein, Amyloid-β

List of Abbreviations

ABC: ATP binding cassette
ACAT: Cholesterol acyltransferase
AChE: Acetylcholinesterase
AD: Alzheimer's Disease
Aβ: Amyloid – beta
APP: Amyloid Precursor Protein
APoE: Apolipoprotein E
ApoJ: Apolipoprotein J
ATP: Adenosine triphosphate
BBB: Blood-Brain Barrier
CDK5: cyclin-dependent protein kinase 5
CDR: Clinical Dementia Rating
CETP: Cholesteryl ester transfer protein
ChEIs: Cholinesterase inhibitors
CM: Chylomicrons
CSF: Cerebrospinal Fluid
CNS: Central Nervous System
CRBP: Cellular retinol-binding protein
CTE: Chronic Traumatic Enchepahlopathy
DHA: Docosahexaenoic acid
DGAT: Diacylglycerol acyltransferase
DTI: Diffusion Tensor Imaging
EEG: Eletroencephalography
EPA: Eicosapentaenoic acid
EOAD: Early-onset Alzheimer's disease
ER: Endoplasmatic Reticulum
FA: Fatty acid
FFA: Free Fatty Acids
FABP: Fatty acid-binding protein
FASN: Fatty Acid Synthase
FLAIR: Fluid Attenuated Inversion Recovery
FATP: Fatty acid transport protein
GSK- 3β: glycogen synthase kinase-3β

HDL: High-density lipoprotein
HIF-1α: Hypoxia-inducible factor
HMG-CoA: Hydroxymethylglutaryl-coenzyme A
HP-β-CD: 2-hydroxypropyl-β-cyclodextrin
LD: Lipid Droplets
LPC: Lysophosphatidylcholine
LOAD: Late-onset Alzheimer's disease
LRAT: Lecithin Retinol acyltransferase
LRP1: Low density lipoprotein receptor-related protein 1
MRI: Structural Magnetic Resonance Imaging
MUFA: Monounsaturated Fatty Acids
NMDA: N-Methyl-D-aspartate receptor
NPC1L1: Niemann-Pick C1 like 1
n-3 PUFA: omega-3 polyunsaturated fatty acids
n-6 PUFA: omega-6 polyunsaturated fatty acids
PC: Phosphatidylcholine
PE: Phosphatidylethanolamine
PET: Positron Emission Tomography
PI: Phosphatidylinositol
PICALM: Phosphatidylinositol binding clathrin assembly protein
PKA: cAMP-dependent protein kinase
PLA2: Phospolipase A2
PLD: Phospholipase D
PLC: Phospholipase C
PP-2A: Protein phosphatase 2A
PPARα: Proliferator-activated receptor-α
PS1: Presenilin I
PS2: Presenilin II
PUFA: Polyunsaturated fatty acids
RNS: Reactive nitrogen species
ROS: Reactive oxygen species
sAPP-α: soluble APP-α
SFA: Saturated fatty acids
SMase Sphingomyelinase
SMs: Sphingomyelins

SP: Sphingolipids

SPT: Serine palmitoyltrasnferase

SR-B1: Scavenger receptor class B type 1

TAG: Triglycerides

TBI: Traumatic Barin Injury

TFA: Trans fatty acids

TLR4: Toll-like receptor 4

TREM2: Triggering receptor expressed on myeloid cells 2

VLDL: Very low density Cholestrol

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1. Introduction

1.1. Background on Alzheimer's Disease and Dementia

Neurodegenerative diseases affect millions of people worldwide and are the leading cause of physical and cognitive disability across the globe, currently, affecting approximately 15% of the worldwide population. These numbers rose over the past 30 years, with the burden of chronic neurodegenerative conditions being expected to at least double over the next two decades. This evolution can largely be attributed to the expansion of the aging population, making it a huge challenge to keep neurological care accessible to everyone. (1) Among the neurodegenerative diseases, Alzheimer's disease and Parkinson's disease are the most prominent ones, with Alzheimer's being the leading global health hazard in the aged population, with approximately 50 million people inflicted with this disease or related dementia. (2)

These diseases are usually characterized by a gradual loss of neuronal function in the brain or peripheral nervous system, leading to a progressive decline in cognitive function, movement control, and other neurological functions. Even though there exist therapies able to relieve some symptoms, it's still not yet possible to slow down its progression or obtain a cure. (3)

What became known as Alzheimer's disease (AD), was discovered on the 3rd of November of 1906, by a clinical psychiatrist and neuroanatomist named Alois Alzheimer. He described a 50-year-old woman whom he had followed from her admission for paranoia, progressive sleep and memory disturbance, aggression, and confusion, until her death 5 years later. His notes reported a peculiar severe disease process of the cerebral cortex with distinctive plaques and neurofibrillary tangles in the brain histology. (4)

AD is the most common type of dementia in order of occurrence, accounting for 60–70% of all cases, and besides its slow progress, there are three identifiable clinical stages.

In the mild stage of Alzheimer's disease, individuals have trouble with recent memories but have minimal difficulty recalling distant memories. They can still live independently but may start to have issues with speech, memory, misplacing objects, and planning. Additionally, they may experience neuropsychiatric symptoms such as anxiety, apathy, irritability, and depression. (5)

The moderate stage of Alzheimer's disease is typically the longest period of the disorder and can last for years. During this stage, patients experience problems with episodic memory, but they may still remember important details about their lives. All aspects of cognitive functions are affected. These patients may require more care and symptoms such as forgetfulness of events or personal history, mood, and behaviour changes, especially in challenging situations, will become more noticeable. (5)

In the late stages of severe Alzheimer's disease, patients typically require extensive assistance with their daily activities and personal care. Their previous skills continue to decline, and they lose the ability to manage their environment and movement, including walking and sitting. Patients often become mute, incontinent, and bedridden. This stage of the disease is associated with multiple complications such as immobility, deep venous thrombosis, malnutrition, risk of aspiration during meals, and infections, which can directly lead to death. (5)

As we age, Alzheimer's disease can develop as a result of various factors such as genetics, environmental influences, and many other factors, such as apolipoprotein and lipid transporter carrying status and dietary lipid content.

As science has advanced, we've gained deeper insights into our world and ourselves. For example, we now know that approximately 60 percent of the human brain is made up of fat (6). These fats are part of a larger group of lipids that cannot be manufactured by the body and must be acquired through diet. It's therefore essential to make informed choices about the types of fats we consume to maintain good health. Beyond their structural brain function, fats also play a role as neurotransmitters and many other functions in the central nervous system (CNS).

Fats are a subset of lipids, which are a diverse class of organic compounds characterized by their insolubility in water and solubility in organic solvents. These molecules are essential components of cellular structures and perform a multitude of functions within biological systems. Typically composed of carbon, hydrogen, and oxygen atoms, lipids encompass a broad spectrum of substances, including fats, oils, waxes, certain vitamins, hormones, and integral components of cellular membranes. (7)

Their roles range from energy storage and structural integrity to signaling and protection, underscoring their fundamental importance in maintaining cellular and systemic homeostasis.

1.2. Importance of Lipid Alterations in Alzheimer's disease pathogenesis

As we age, the distribution of lipids in our body changes. It is known, now, that dysregulations in lipid metabolism in the brain are a major risk factor for many neurodegenerative diseases such as Dementia, Alzheimer's, Parkinson's, and Amyotrophic lateral sclerosis. (8)

It is for long known that lipid accumulation occurs in AD neuropathology. (9) However, studies aiming to understand the impact of lipid imbalance on AD are recent. (10) Studies consistently demonstrate changes in various lipid classes during the early stages of AD. Moreover, research has shown that lipid metabolism interacts complexly with key AD pathogenic mechanisms such as amyloidogenesis, bioenergetic deficit, oxidative stress, neuroinflammation, and myelin degeneration. (11)

During the initial two decades of human life, there is an increase in the amount of cerebral lipids, which subsequently begins to decrease after the age of 50. (12) This phenomenon can be attributed to the aging process that leads to a gradual decline in cognitive abilities. This decline is caused by the elevation of systemic free fatty acids (FFA) since there are age-related differences in the lipidic composition in different brain areas. For example, if we compare the brain of a mid-life male and the one of a younger male, the amount of saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA) is increased in the mid-life one, while the polyunsaturated fatty acids (PUFA) decrease. (13,14)

1.3. Purpose of the thesis

The main goal of this thesis is to investigate the complex relationship between changes in lipids and Alzheimer's disease. The focus is on understanding the role of lipids in the development, diagnosis, and possible treatment of AD. By exploring how irregularities in lipid regulation contribute to the onset and advancement of Alzheimer's, this thesis seeks to offer a thorough comprehension that could lead to new therapeutic approaches targeting lipid metabolism.

2. Alzheimer's and Dementia – The impact on our society

2.1. Overview of the societal impact of Alzheimer's disease and dementia

Over the last decades, all industries have been affected by the technological revolution and, consequently, society is presented with innovations in different areas, especially in health, which has managed to find treatments for various diseases and improve timely responses to global crises, thus minimizing the number of deaths worldwide and significantly increasing the average lifespan over the last 70 years. However, the fact that a person can reach older ages is still not seen in full favor by everyone as they are exposed to diseases that develop as we age, as is the case with Alzheimer's and Dementia. (15)

Despite all the scientific advances, the cure for Alzheimer's and Dementia, unfortunately, is late to appear, and according to the World Health Organization (WHO), there are currently more than 55 million people living with dementia around the world. Although this number represents less than 1% of the world's population, surpassing 8 billion this year, approximately 10 million new cases appear every year, equivalent to a new case every three seconds. (16,17)

Although there are a higher number of cases among the elderly, Dementia is not an inevitable consequence of aging and can also be diagnosed in younger people. By affecting memory and other cognitive abilities, it ends up being the biggest cause of disability and dependence in those diagnosed. With an estimate that by 2050 it will reach more than 130 million people, Dementia will become one of the most significant crises at a global level of the 21st century, having a tremendous impact not only on individuals but also on a social, economic, or public health level. (18)

2.2. Economic, social, and healthcare burden

Over the past century, society's healthcare has improved, contributing to longer lives. However, as our societies age and the number of people with dementia increases, the societal impacts spanning healthcare systems, economic burdens, and social dynamics will become more profound.

2.2.1. Economic

The overall consequences of dementia are challenging for any healthcare system. Aside from understanding the impacts on people with dementia and their families, data on resource use and costs in combination with prevalence figures are essential for planning care infrastructure.

The costs of dementia care are categorized into direct medical costs, direct social (non-medical) costs, and informal care costs. Direct medical costs include expenses for hospital care, medications, diagnostic tests, and clinic visits. Direct social costs cover community-based services to assist with daily living activities and long-term institutional care. Informal care costs are more difficult to measure and are typically estimated based on the time family members or informal caregivers spend providing support for basic and instrumental activities of daily living, including supervision time. (15)

In 2015, the total global cost of dementia was estimated at US$ 818 billion, with 40% of this amount related to informal care, 40% to the social care sector, and 20% to the medical sector. If dementia care costs were considered a country, it would be the world's 18th largest economy, surpassing companies like Apple, Google, and Exxon. By 2030, it is estimated that the cost of caring for people with dementia will rise to US$ 2 trillion, which could hinder global social and economic development and overwhelm health and social care systems. (16)

2.2.2. Healthcare

Dementia severity significantly influences costs, with annual per-patient expenses increasing from almost €15k for mild dementia to €35k for severe dementia. The global cost of dementia heavily impacts care systems, particularly in Low-Middle-Income Countries where long-term care systems are inadequately prepared, burdening carers and families. Current cost estimates likely underestimate the true economic impact due to the complexity of calculating global costs and the under-detection of dementia cases. (15)

Research and innovation are essential to reduce dementia incidence and improve patient lives, but these efforts require substantial funding and infrastructure. High research and development costs, driven by low success rates and long development times, pose additional challenges. (15)

2.2.3. Social

Family members and friends significantly impact the societal costs of dementia by providing extensive unpaid informal care. Most informal carers are family members who generally find the experience positive. However, it can also be stressful, leading to issues such as coping difficulties, burden, stress, depression, reduced social networks, and health problems. (19)

People with dementia and their carers often face stigma, discrimination, and human rights violations due to a lack of awareness and understanding. This can hinder access to diagnosis and care, with dementia frequently misconceived as a natural part of aging. Improving public understanding through accurate information is crucial to dispelling these myths and stereotypes. (15)

2.3. Implications for individuals and caregivers

AD has profound health implications, leading to progressive memory loss, impaired reasoning, and difficulty with language and communication, which affects the ability to perform everyday tasks and make decisions. A large part of the population with this disease tends to depend on the family member and/or caregiver which will impose a severe burden not only upon patients but also their caregivers, affecting their health, daily life, emotional well-being, and social interactions. (19)

AD affects each person in different ways, depending on its cause and other health factors. As time passes and symptoms appear and worsen, other aspects of personal life will be affected. In daily life, the loss of independence becomes evident as cognitive and physical abilities decline, requiring assistance with activities of daily living. Managing daily routines becomes challenging and constant supervision becomes necessary to ensure safety and well-being. (20)

Emotionally and psychologically, the awareness of cognitive decline can lead to feelings of frustration, confusion, anxiety, and depression, exacerbated by social isolation and the loss of one's sense of self. Individuals may experience significant behavioral changes, including agitation, aggression, mood swings, and hallucinations, distressing both the person and their caregivers. The need for help with personal care and the inability to perform once-familiar tasks can lead to a loss of dignity and self-esteem. (20)

Social implications include strained relationships with family and friends, and communication difficulties and behavioral changes further complicate relationships. Individuals with Alzheimer's often withdraw from social activities and interactions due to embarrassment, fear, or difficulty following conversations, leading to isolation and loneliness. The social stigma associated with Alzheimer's can result in misunderstanding and discrimination, preventing individuals from seeking the help they need. (15,20)

Financially, the cost of medical care, medications, and professional caregiving can be substantial, with long-term care facilities and specialized treatments adding to the financial burden. Individuals may have to retire early or stop working due to the disease, leading to a loss of income, and families may face financial strain as they take on caregiving responsibilities and related expenses.(21,22)

As regards the carers, they need to prioritize self-care due to the physical and emotional demands of caregiving. Increased care demands can lead to burnout, making it crucial for carers to take time for themselves. Without self-care, carers may experience emotional issues like guilt, grief, anger, and feelings of abandonment, often due to a lack of understanding from others. (23)

Burnout can cause physical, emotional, and mental fatigue, leading to depression and anxiety, which may negatively affect the quality of care provided. Carers might notice decreased patience and increased demands on their loved ones. Recognizing changes in their attitude and addressing their own feelings is essential for maintaining good care. (23)

Carers should continue activities they enjoy and learn to ask for help to lighten their burden. Preventing carer burnout is vital to ensure they can remain effective and compassionate caregivers. (23)

3. Pathogenesis of Alzheimer's Disease

3.1. Mechanisms underlying Alzheimer's disease pathology

Despite extensive research, the exact pathogenesis of Alzheimer's disease is not yet fully understood. Currently, the amyloid cascade, tau protein, neuroinflammation, metal ions, and oxidative stress hypotheses are the main focus of research on AD mechanisms. (24)

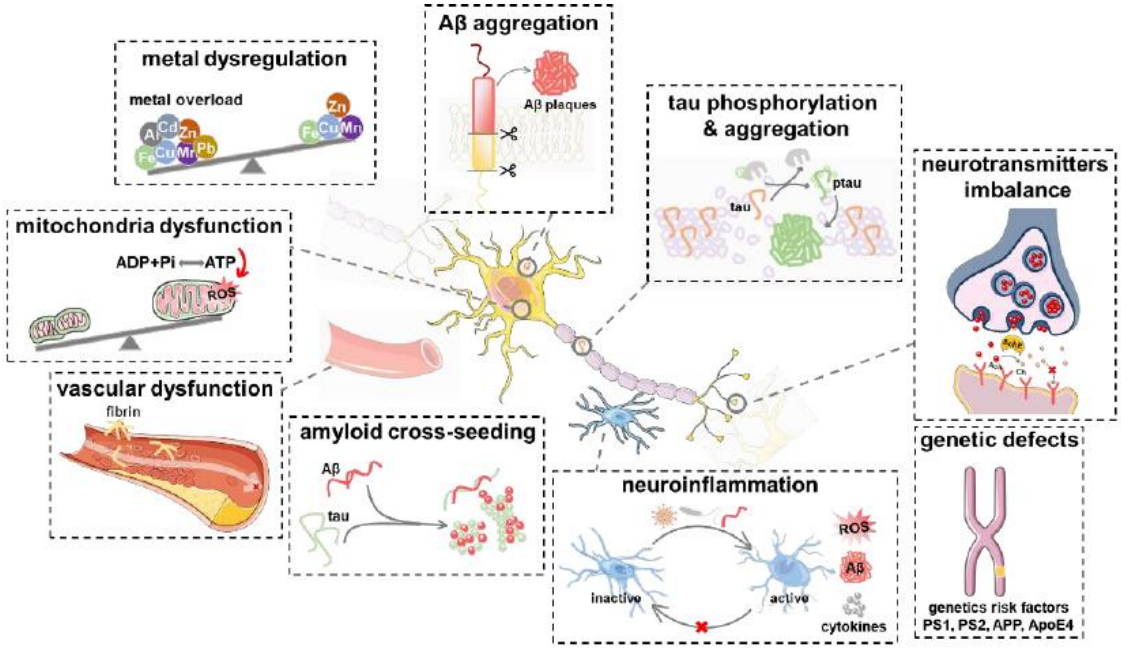


Figure 3.1 - Different plausible AD mechanisms. Such as Amyloid-beta (Aβ) aggregation, tau phosphorylation and aggregation, neurotransmitters imbalance, genetic defects, neuroinflammation, amyloid cross-seeding, vascular dysfunction, mitochondria dysfunction, and metal dysregulation. (25)

3.1.1. Oxidative stress

Oxidative stress plays a crucial role in connecting these different hypotheses and mechanisms of AD, as it is a complex process that leads to neuronal damage through various pathways. (24) Oxidative stress refers to the oxidative damage of cell components caused by the accumulation of Reacive Oxygen species (ROS) and reactive nitrogen species (RNS), which overwhelm the cellular antioxidative capacity. (26) Neurons are particularly vulnerable to an oxidized redox environment compared to glial cells due to their limited antioxidative defenses. In the brain, oxidative stress is primarily manifested by lipid peroxidation, given the brain's high content of oxidation-prone lipids. In AD brains, amyloid plaques and their immediate surroundings are marked by the presence of oxidized lipids, whereas cognitively normal individuals exhibit lower levels of oxidized lipids, even in the presence of plaques. (27) For instance, ceramides not only directly affect Aβ but also promote ROS generation in AD, since H2O2 can activate sphingomyelinases directly or indirectly (via cPLA2 and arachidonic acid), leading to sphingomyelin hydrolysis and ceramide production, forming a never-ending cycle. (26,28)

3.1.2. Aβ aggregation

In AD two main proteins play crucial roles. One of these proteins is the Amyloid protein, which originates from the amyloid precursor protein (APP), a common protein in the CNS. Amyloid can generate either a healthy or toxic form known as amyloid-beta (Aβ). Typically, in healthy brains, the amyloid-beta is cleared before causing damage. However, in AD, Aβ aggregates into amyloid plaques, contributing to neuronal inflammation, and promoting abnormal production of tau proteins. (29,30)

Aβ aggregation, also known as amyloidopathy, represents a prominent mechanism in AD, characterized by the deposition of amyloid beta peptide as senile plaques in neuronal cells. The APP, a transmembrane protein, generates Aβ peptides of either 40 or 42 amino acids. $A\beta_{42}$ is highly toxic and is produced via a pathway involving β-secretase 1, rather than the α- and γ-secretases typical of $A\beta_{40}$ formation. (31,32) Under normal circumstances, Aβ peptides are released into the extracellular space and are transported and degraded by the lipoproteins ApoE2 and ApoE3. However, $A\beta_{42}$ has affinity for ApoE4, which contributes to its aggregation within the CNS extracellular regions. In normal conditions, during Aβ generation, the level of neprilysin increase to facilitate Aβ turnover. However, mutations disrupt this process, leading to the progressive accumulation of Aβ and the onset of AD.(32,33)

Several studies indicate that cholesterol levels impact the amyloidogenic pathway, with high cholesterol enhancing the activity of β- and γ-secretases, while low cholesterol inhibits their activity.(34) Research demonstrates that reducing cholesterol synthesis in astrocytes significantly lowers amyloid and tau pathology in a mouse model of Alzheimer's disease. This reduction in pathology is due to decreased cholesterol levels in neurons, which cause APP to move out of lipid rafts where β- and γ-secretases are located. Outside of these lipid rafts, APP is instead processed by α-secretase into the neuroprotective and non-amyloidogenic soluble APP-α (sAPP-α) (35,36)

Studies have shown that ceramide plays a critical role in the formation and aggregation of Aβ in AD. In the brain, ceramides can disrupt mitochondrial function, exacerbate endoplasmic reticulum (ER) stress, produce excessive ROS, and disturb protein homeostasis. These disruptions lead to abnormal Aβ accumulation and neuronal apoptosis.(37) The levels of ceramide also influence Aβ content, directly impacting AD progression. Sphingolipid hydrolases positively regulate γ-secretase activity and Aβ secretion. Ceramide promotes Aβ production by stabilizing β-secretase, which is crucial for Aβ formation. (38) Additionally, ceramide induces oxidative stress responses, activating sphingomyelinase (SMase) and

catalyzing sphingomyelin breakdown to generate more ceramide. This creates a vicious cycle that increases Aβ deposition, triggers neuronal cell death, and exacerbates neuroinflammation, thereby worsening AD pathology. (39,40)

3.1.3. Tauopathies

Other key protein that presents changes in AD is the Tau protein, which normally plays a crucial role in maintaining the structural integrity of axons by associating with microtubules. However, in AD, Tau proteins can become dysfunctional and aggregate, forming neurofibrillary tangles. These tangles are toxic to neurons, leading to their eventual death. When a neuron dies, a chain is broken, disrupting communication pathways and resulting in memory gaps characteristic of AD. (41,42)

Tauopathies, characterized by tau phosphorylation and aggregation lead to the formation of tangles in neuronal cells, consequently leading to neurodegeneration. (43) Usually, six isoforms of the tau protein, which vary from each other based on the presence or absence of one or two inserts (29 or 58 amino acids) in their N-terminal sequences, and the inclusion or exclusion of a long microtubule-binding repeat domain in their C-terminal half. (32) The increased glycosylation of tau protein increases its susceptibility to phosphorylation by various protein kinases, such as cAMP-dependent protein kinase (PKA), glycogen synthase kinase-3β (GSK-3β), and cyclin-dependent protein kinase 5 (cdk5). However, this glycosylated tau protein also becomes more sensitive to the downregulation of dephosphorylation by protein phosphatase 2A (PP-2A). In Alzheimer's disease, the activity of PP-2A is significantly reduced, which may be one of the factors contributing to the abnormal hyperphosphorylation of tau protein. (32,44)

Even though the connection between tau protein and lipids is primarily indirect, some studies suggest that brain cholesterol accumulation and high dietary cholesterol are associated with increased tau phosphorylation and aggregation. These studies showed that neurons with tangles contain higher levels of unesterified cholesterol compared to neighbouring tangle-free neurons in the brains of AD patients. (45)

The interaction between tau proteins and cellular membranes is important in causing neurotoxicity in AD. Research has shown that when tau binds to membranes, it can induce neurotoxicity. Tau-phospholipid complexes, which can be identified by the MC-1 antibody, form long tubular and filament-like aggregates in slightly acidic conditions, displaying pathological properties. These complexes can enter primary hippocampal neurons through endocytosis, leading to cell damage. (46) Additionally, insoluble aggregates of fibrillar tau can interact with lipid bilayers, changing membrane conductance. This alteration can lead to increased calcium influx through voltage-gated calcium channels, elevated levels of reactive oxygen species, and activation of NADPH oxidase. This sequence of events ultimately leads to the death of primary cortical neurons and astrocytes. (47) Moreover, hyperphosphorylated tau is present in both pre- and post-synaptic compartments in synaptosomes isolated from AD patients, disrupting synaptic function and contributing to cognitive deficits.(46,47)

3.1.4. Neuroinflammation

Neuroinflammation is usually triggered in response to infection, trauma, and toxic substances, with the evolvement of neuronal cells, microglia, and astrocytes. When Aβ and tau tangles form in the brain, they trigger an inflammatory response from the surrounding glial cells. This leads to a loss of their normal function and an increase in proinflammatory activity, which can cause further damage to the neurons. In cases of neuroinflammation, specific inflammatory mediators like TNF-α, IL-6, IL-1β, and COX-2 are present in the blood and brain samples of patients with Alzheimer's disease. (32,48)

Research has shown that a combination of IFNγ with either TNFα or IL-1β could stimulate the production of Aβ through the cleavage of the immature APP molecule mediated by β-secretase. However, a study by Holmes et al. has found that an increase in serum TNF-α is strongly correlated with a faster cognitive decline rate in AD patients compared to the low TNF-α level in the control group, which showed no cognitive decline over the same period. (49)

Lipid rafts, which are rich in cholesterol and sphingolipids, play a crucial role in initiating inflammatory responses in glial cells. High cholesterol levels in these lipid rafts are associated with the clustering of inflammatory proteins, leading to increased inflammation. (50) Collectively, lipid metabolism contributes to chronic and unresolved neuroinflammation in AD through the production of both pro-inflammatory and pro-resolving lipid-derived messengers. (26)

The reduction of sphingomyelin levels in AD brain tissue result in its hydrolysis by sphingomyelinase, leading to increased ceramide production.(51) This rise in ceramide activates the NF-κB signaling pathway in microglia, causing the glial response to shift towards inflammation and triggering the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 from astrocytes, thus inducing neuroinflammation. (52)

Serine palmitoyltransferase (SPT), the enzyme responsible for the initial step in de novo ceramide synthesis, when inhibited, prevents astrocytes from producing proinflammatory mediators such as IL-1β, TNF-α, iNOS, and COX-2. This inhibition also decreases the secretion of pro-inflammatory cytokines by astrocytes and reduces caspase-3 neurotoxicity. (53)

During chronic CNS inflammation, both ceramide and its derivative, lactosylceramide, increase in astrocytes, worsening inflammation and neurodegeneration. As a result, abnormal ceramide metabolism in glial cells is closely linked to the neuroinflammatory response, playing a critical role in the pathogenesis of AD. (40,54)

3.1.5. White matter alterations

White matter, constituting about 40% of the human brain, is primarily composed of myelinated neuronal axons, where myelin facilitates rapid nerve conduction. Myelin is predominantly lipid, making up 80% of its dry weight. (26) Accumulation of fatty acids and glycosphingolipids is linked to myelin dysfunction in various inherited diseases and is also observed in AD. (55) Both glycolipids and phospholipids, crucial components of myelin, depend on fatty acids for their synthesis. Disruptions in fatty acid metabolism contribute to AD-related white matter abnormalities. Recent studies indicate that fatty acid synthesis in oligodendrocytes is essential for proper myelination. (56,57)

Astrocytes also play a role by transporting lipids to oligodendrocytes, though excess saturated fatty acids from reactive astrocytes can be toxic and induce oligodendrocyte death. (58) While TREM2 is important for clearing myelin debris and supporting remyelination by regulating lipid metabolism in microglia, its deficiency disrupts lipid metabolism, further contributing to AD pathology. (59)

3.1.6. Blood-Brain Barrier

The blood-brain barrier (BBB) plays a crucial role in both separating and connecting the brain to the peripheral circulation, enabling the transcytotic exchange of substances, including lipids.(60) BBB dysfunction appears in the early stages of Alzheimer's disease (AD), independent of amyloid-beta (Aβ) or tau biomarker changes, with the endothelial transcytosis and clearance of Aβ across the BBB being mediated by lipid-related genes such as Phosphatidylinositol binding clathrin assembly protein (PICALM) and Low density lipoprotein receptor-related protein 1 (LRP1). (26) Although the exact contribution of lipid metabolism to

BBB disruption in AD is not fully understood, recent studies indicate that lipid profiles influence BBB function. This is evidenced by increased BBB permeability and decreased DHA levels in AD brains. (61) Additionally, obesity-associated high levels of circulating saturated fatty acids lead to elevated cerebrospinal fluid (CSF) levels of palmitate, increased BBB permeability, and subsequent neuroinflammation, impairing synaptic and cognitive functions. (26)

3.2. Genetic and environmental factors contributing to disease development

Several risk factors are said to influence AD, including age, familial inheritance, exposure to metals, traumatic brain injury, and other associated co-morbidities such as vascular disease and diabetes.

3.2.1. Age

With the advancing age, in a cognitively normal brain, there is an age-related reduction in brain volume and weight, enlargement of ventricles, and loss of synapses and dendrites in selected areas, with the appearance of senile plaques and neurofibrillary tangles. (62)

According to studies, the prevalence of AD increases to an estimated 19% in individuals 75-84 years of age and to 30-35%, possibly up to 50% for those older than 85 years. (63,64) Some lipidic alterations emerge during normal brain aging, such as alterations in the sphingolipid and cholesterol metabolism, that are also common in the brains of AD patients resulting in the accumulation of long-chain ceramides and cholesterol. (65)

3.2.2. Genetics

According to recent studies, there have been identified over 30 genes that may contribute to the development of AD. This disease can be divided into late-onset AD (LOAD) and Early-onset AD (EOAD), each of which is associated with different genetic risk factors.

EOAD is mostly inherited by gene mutation on Aβ APP located at chromosome 21, presenilin I (PS1) at chromosome 14, and presenilin II (PS2) at chromosome 1 (25,66). These genes will accelerate the proteolytic cleavage of APP toward amyloidogenic pathways, leading to an excessive production of Aβ.

LOAD is a complex stage of AD, evolving various gene mutations/variants. The most prominent one is ApoE4, located on chromosome 19, influencing almost every node and pathway related to AD.

3.2.2.1. APoE4

Beyond its role in regulating Aβ production and clearance, the pathological impact of ApoE4 is significantly influenced by lipid-centric mechanisms. (67) Compared to ApoE3, ApoE4 exhibits a loss-of-function as an intercellular lipid carrier. This results in ApoE4 carriers having higher plasma levels of total cholesterol and triglycerides (TAG), but reduced levels of high-density lipoprotein (HDL) cholesterol.(68) These lipid imbalances contribute to the pathogenesis of Alzheimer's disease by affecting lipid homeostasis, which in turn influences Aβ aggregation and neuroinflammation. (25)

3.2.2.2. TREM2

TREM2, found primarily on the surfaces of microglia, plays a critical role in mediating phagocytosis and the inflammatory response in the brain's resident myeloid cells. (69,70) Additionally, a rare TREM2 variant (R47H) is linked to a significant increase in AD risk.

Beyond its interaction with Aβ, TREM2 acts as a sensor for phospholipids, lipoproteins, and apolipoproteins, highlighting its broader role in lipid metabolism and AD pathogenesis. (71,72)

3.2.2.3. Clusterin (ApoJ)

Clusterin has been identified as a gene associated with an increased risk of Alzheimer's disease. In addition to its role as a molecular chaperone in protein folding and its impact on the aggregation of beta-amyloid, clusterin is also involved in the transport and metabolism of lipids in both the brain and the peripheral tissues. (26,73)

3.2.2.4. Picalm

PICALM, a major AD risk gene, is crucial for clathrin-mediated endocytosis, which facilitates the internalization and transport of proteins and lipids in lipoprotein particles. (74) PICALM's role in Aβ clearance is particularly significant and is mediated by its binding to the LRP1. This interaction highlights the importance of lipid and protein transport mechanisms in AD pathogenesis and the potential impact of genetic factors on disease progression. (75)

3.2.2.5. ABCA

ABCA1 promotes the release of cholesterol and phospholipids by transferring them to lipid-free lipoproteins. ApoE is the primary protein used for this lipidation process in the brain. (76) A loss-of-function mutation in the ABCA1 gene is linked to lower plasma levels of ApoE and a higher risk of AD. (77) The ABCA7 gene, also involved in cholesterol and phospholipid transport, is associated with AD through various genetic and epigenetic alterations, including single nucleotide polymorphisms, variants, alternative splicing, and methylations. These alterations contribute to ABCA7's loss-of-function, disrupting lipid and Aβ metabolism, and increasing the risk of AD. (78,79)

3.2.3. Metals

Metal ions such as iron, zinc, copper, and calcium, are essential elements for regulating the human body functions. In AD, these metals' deficiency, overproduction, and mislocalization are associated with Aβ deposition and tau accumulation/ hyperphosphorylation. (25)

The two redox-active transition metals, iron, and copper are essential for oxygen delivery for brain metabolism and enzyme catalysis for neural function. Dysregulation of Fe3+/Fe2+ and Cu2+/Cu+ results in the formation of H2O2 and ROS, leading to an increase in oxidative burden and subsequent neuronal dysfunction and cell loss in AD brains. Excessive amounts of iron and copper can directly interact with Aβ and tau to form complexes, which can penetrate neurons and trigger ROS within different neuronal sub-compartments. Additionally, they can indirectly enhance Aβ production by activating β-secretase/inhibiting α-secretase and tau production by activating GSK3β/CDK5. (80,81)

Metallothionein regulates zinc levels by exchanging copper in the Aβ-Cu complex, inhibiting ROS damage. Zinc deficiency not only hinders normal zinc-related enzymatic activities but also increases ROS risk. Similarly to iron and copper, zinc also shows a high binding affinity to Aβ and tau. When zinc binds to amyloids, zinc-amyloid complexes inhibit APP ferroxidase activity, but increase levels of iron and ROS, as well as the production of Aβ and tau. (82,83)

Some toxic non-essential metals, like aluminium, lead, and cadmium, obtained through oral intake or environmental pollutants, are suspected to mess with homeostasis at cellular and organismal levels, affecting certain risk factors, including Aβ and tau aggregation, microglia activation, proinflammatory cytokines overproduction, and ROS. (25,82)

3.2.4. Traumatic Brain Injury

Repeated brain injury can impact the development of Alzheimer's disease. When traumatic brain injury (TBI) occurs more frequently, it leads to an increased production of APP in response to neuronal injury, which results in the accumulation of Aβ. The connection between TBI and AD is further highlighted by the identification of chronic traumatic encephalopathy (CTE), a neurodegenerative condition believed to be a direct result of repetitive brain injury. (64,84)

3.2.5. Cardiovascular Diseases

Cardiovascular diseases, which are characterized by the accumulation of fibrinogen, a major protein involved in blood clotting, can slow down cerebral blood flow and lead to the production of hypoxia-inducible factor (HIF-1α). This factor further activates γ-secretase, increasing the production of Aβ, which is associated with AD. As cerebrovascular circulation is damaged or ages, it becomes more difficult to clear Aβ from the brain via blood vessels. This leads to increased Aβ concentration in the brain, creating a vicious cycle of Aβ build-up. (85,86) Another plausible mechanism that has been proposed is that high blood cholesterol levels increase the risk of cardiovascular diseases, since studies have shown that the homeostasis of lipids in the brain, both cholesterol and sphingolipids, are crucial to the lipid composition of the cell membrane and the formation of lipid rafts connected with the formation and toxicity of Aβ. (87)

3.2.6. Diabetes

Type 2 diabetes mellitus has also been linked to AD, since insulin, which has a central role as a neuromodulator, has its expression reduced. Some studies showed an association between hyperinsulinemia and hyperglycemia and AD. The insulin resistance results in an accumulation of sphingolipids (SP), especially in individuals expressing APOE allele ε4, leading to a breakdown of the brain metabolism and cognitive function. (88) Insulin is able to affect the electrochemical and biochemical action of neurons, from neurotransmitters associated with memory and learning to the enzymes that participate in the metabolism of Aβ. (89) Another study, using rats fed with a high-fat diet, including cholesterol, showed an increased cognitive decline, characterized by Aβ deposition. (87,90)

3.2.7. Diet

Some ecological and observational studies showed that dietary factors seem to affect the risk of AD. For example, when Japan made the nutrition transition from the traditional Japanese diet to the Western diet, AD rates rose from 1% in 1985 to 7% in 2008. Foods protective against AD include fruits, vegetables, grains, low-fat dairy products, legumes, and fish, whereas risk factors include meat, sweets, and high-fat dairy products. (91)

Another study, using a triple transgenic mouse model, showed that high-fat consumption combined with a lower polyunsaturated fatty acid ratio promoted Aβ and a tau-immunoreactive pathology similar to that of AD. (92) Moreover, research showed that statin use may reduce the risk of AD independent of the possession of *APOE* allele ε4, but the strength of this link reduces with age. (64,93)

4. Lipids in the Human Body, A General Overview

Lipids are a key component of the human body, therefore they play a big role in defining our health and well-being, with various changes that can improve or worsen the physiologic pathways of our being. (94)

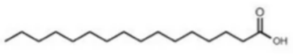
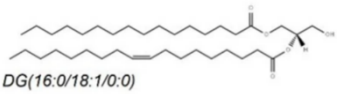
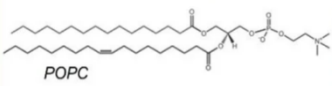
Lipids are defined by their insolubility in water and solubility in nonpolar organic solvents. This large family includes fats like triglycerides, fatty acids and their derivatives like monoglycerides and phospholipids, and sterol metabolites like cholesterol. (95)

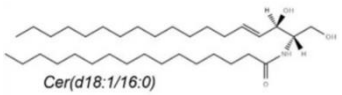
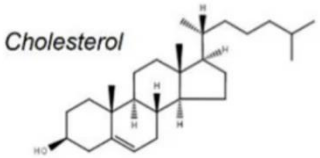
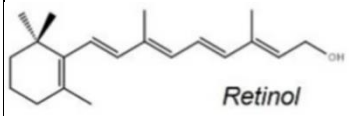
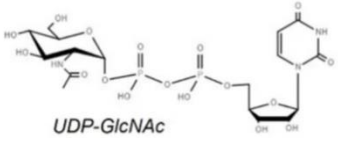
They play several roles in our body, such as providing energy and maintaining the body temperature, acting as a chemical messenger. They are also involved in the formation of the membrane layer and prostaglandins which can cause various inflammatory effects such as vasodilation, fever, and some allergic reactions. (96)

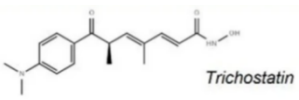
4.1. Lipids classification

An abysmal number of different lipids are being synthesized, working hand to hand with the produced proteins, enzymes, and receptors, in different procedures and functions. The majority of these lipids can be classified under the LIPID MAPS classification system. (97)

Table 4.1 **Lipids Classification**

Classification	Description	Structure Examples	Reference
Fatty Acyls	Fatty acyls are a diverse group of molecules synthesized by chain elongation of an acetyl-CoA primer with malonyl-CoA (or methylmalonyl-CoA) groups. This group consists of a hydrocarbon chain with a carboxyl group that can vary in length, be branched or linear, contain double bonds, linked to a diverse range of substituents. This category contains not just fatty acids but also other functional variants such as alcohols, aldehydes, amines, and esters.	 Palmitic acid	(97–101)
Glycerolipids	Glycerolipids include acylglycerols but also encompass alkyl and 1*Z*-alkenyl variants. This group is dominated by the mono-, di- and tri-substituted glycerols, the most well-known being the fatty acid esters of glycerol (acylglycerols).	 DG(16:0/18:1/0:0)	(99,101,102)
Glycerophospholipids	The glycerophospholipids are widespread in nature and are crucial components of the lipid bilayer in cells. These molecules are characterized by the presence of a phosphate (or phosphonate) group esterified to one of the glycerol hydroxyl groups.	 POPC	(99,101,102)

Sphingolipids	Sphingolipids form a diverse group of compounds characterized by a shared sphingoid base backbone. This backbone is produced from serine and a long-chain fatty acyl-CoA through de novo synthesis. Subsequently, it is transformed into various compounds such as ceramides, phosphosphingolipids, glycosphingolipids, and protein adducts. These compounds play a crucial role in the CNS, contributing to tissue development, cell recognition, adhesion, and acting as receptors for toxins.		(99,101–103)
Sterol lipids	Sterols are synthesized through a common biosynthetic pathway via the polymerization of dimethylallylpyrophosphate/isopentenyl pyrophosphate. However, they have a unique fused ring structure, characteristic of this class. The sterol category is primarily subdivided based on biological function, since they are important components of membrane lipids, progestogens, glucocorticoids, mineralocorticoids, and vitamins D.		(99,101,102)
Prenol lipids	Prenols are synthesized from the five-carbon precursors isopentenyl diphosphate and dimethylallyl diphosphate, which are mainly produced via the mevalonic acid pathway. This class includes carotenoids, which are precursors of vitamin A and also possess antioxidant effects. Prenol lipids containing more than 40 carbon atoms are termed as polyterpenes. Another biologically important class of molecules includes quinones, ubiquinones, and hydroquinones, such as vitamin K and vitamin E.		(101,102,104)
Saccharolipids	This group is made of fatty acids that are directly linked to a sugar backbone, forming structures that are compatible with membrane bilayers. The most familiar saccharolipids are the acylated glucosamine precursors of the lipid A component of the lipopolysaccharides in Gram-negative bacteria. They show considerable structural variation		(99,101,102,105)

	among organisms and have complex functions and effects on the GI tract.		
Polyketides	This group consists of molecules derived from the condensation of ketoacyl subunits. Their backbone is modified by glycosylation, methylation, hydroxylation, oxidation, and/or other processes, allowing them to form a diverse group of metabolites from plant and microbial sources. Many commonly used antimicrobial, antiparasitic, and anticancer agents are polyketides or polyketide derivatives. Important examples of these drugs include erythromycins, tetracyclines, nystatins, avermectins, and antitumor epothilones.	 Trichostatin	(99,101,102)

4.2. Influence of Dietary lipids on health

It's widely accepted that our food choices significantly shape our physical and mental well-being. In other words, we are what we eat, and what we eat directly impacts our health and happiness.

Just as humans evolved, so did their lipid intake. We started to ingest more SFA, trans fatty acids (TFA), and omega-6 polyunsaturated fatty acids (n-6 PUFA) instead of omega-3 polyunsaturated fatty acids (n-3 PUFA), and when the Mediterranean diet is compared with the Western diet, it's possible to see a contrast in the ingested lipids. (106)

The Mediterranean diet is known for including healthy fats like eicosapentaenoic acid (EPA) and DHA, which have anti-inflammatory properties. These healthy fats, also known as n-3 PUFA, help to reduce inflammation, suppressing genes involved in inflammation, and affecting lipid raft aggregation and cell signalling. (107) The n-3 PUFA can increase the size of lipid rafts and alter their stability, which promotes the aggregation of cholesterol in the plasma membrane. Additionally, they can suppress downstream activation signalling in CD4+ T cells and IL-2 secretion by suppressing or normalizing the actin cytoskeletal rearrangement. (108)

Meanwhile, the Western diet is known for its constitution with SFA, TFA, and n-6 PUFA which play the opposite role and have pro-inflammatory properties, especially because one of its downstream metabolites is arachidonic acid, which is the primary precursor in the inflammatory cascade (109,110)

5. Lipids pathway in the human body

5.1. Overview of lipid metabolism and pathways

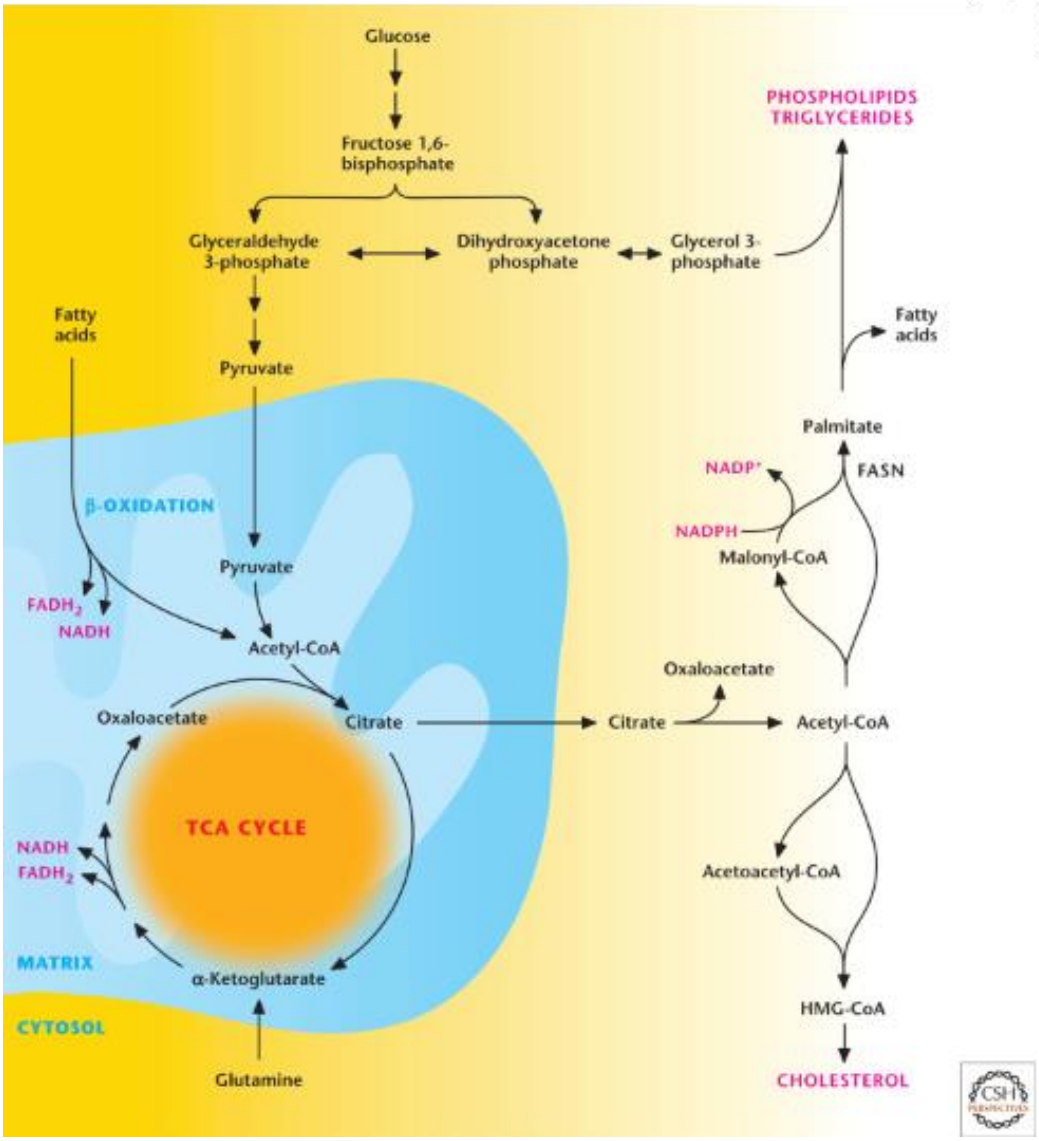


Figure 5.1 Overview of Lipid Metabolism. Lipid synthesis involves the use of dihydroxyacetone phosphate from glycolysis and citrate from the TCA cycle to produce glycerol 3-phosphate and acetyl-CoA. Fatty acid synthase (FASN) converts acetyl-CoA into palmitate, which, combined with glycerol 3-phosphate, forms triglycerides and phospholipids. Acetyl-CoA is also a precursor for cholesterol synthesis. Lipids can be broken down into fatty acids, which are then used by mitochondria in β-oxidation to generate ATP. (111)

The body can obtain lipids from three sources: ingested, stored in adipose tissue, or synthesized in the liver. When we consume fats in our diet, they are digested in the small intestine through a process called lipolysis, which breaks down triglycerides into monoglycerides and free fatty acids. These components then pass through the intestinal wall and are resynthesized into triglycerides and transported to the liver or adipose tissue. Fatty acids are oxidized through β-oxidation, which creates two-carbon acetyl CoA molecules. These molecules can then enter the Krebs cycle to generate adenosine triphosphate (ATP). If there is excess acetyl CoA that overloads the capacity of the Krebs cycle, it can be used to synthesize ketone bodies. When glucose is limited, ketone bodies can be used for fuel. Excess acetyl CoA generated from excess glucose or carbohydrate ingestion can be used for fatty acid synthesis or lipogenesis. Acetyl

CoA is used to create lipids, triglycerides, steroid hormones, cholesterol, and bile salts. (111,112)

5.2. Digestion and Absorption of lipids

The process of lipid digestion in the human body begins with the intake of lipids through the oral cavity, where they get exposed to various lipases in the saliva. As these lipids reach the stomach, the process of emulsification begins, aided by the peristaltic movements. Then the lipidic emulsion reaches the duodenum, where the lipids are mixed with bile and pancreatic fluids. (113)

Emulsification continues in the duodenum walls through processes like hydrolysis and micellization, preparing lipids for absorption through the intestinal wall.

During the process of lipid hydrolysis, larger lipid molecules are broken down into smaller components. The resulting products are then solubilized in micelles, that transport the lipid products to the apical membrane of enterocytes, the cells in the lining of the small intestine responsible for nutrient absorption.

The apical membrane of enterocytes is equipped with several transport proteins that allow for the efficient uptake of different types of lipids. These transport proteins include fatty acid transporters, cholesterol transporters, and other specialized carriers that facilitate the movement of lipids across the membrane and into the enterocyte. (114)

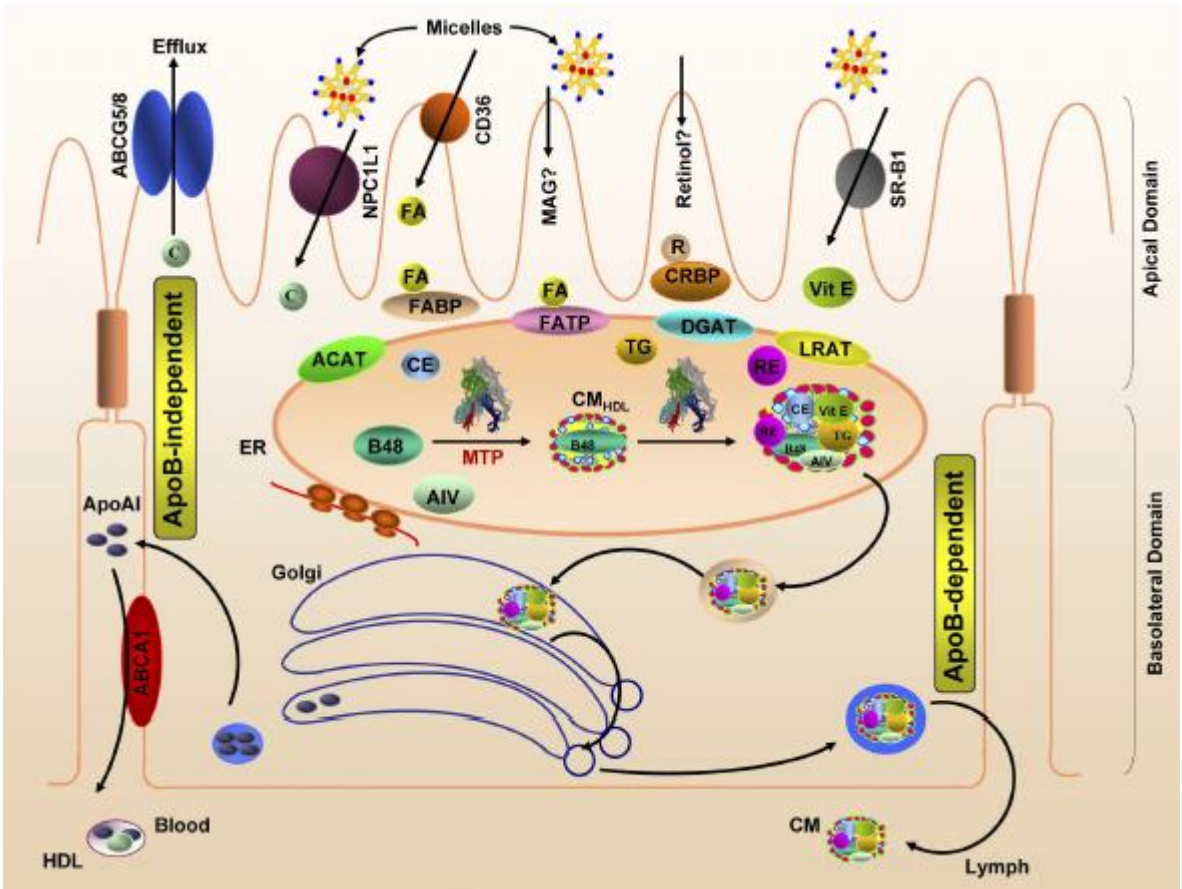


Figure 5.2 Overview of Intestinal Lipid Absorption. Products of lipid hydrolysis are solubilized in micelles and presented to the apical membranes of enterocytes, which contain transport proteins for lipid uptake. Niemann-Pick C1 like 1 (NPC1L1) aids in cholesterol uptake, CD36 and fatty acid transport protein (FATP) handle fatty acids, and scavenger receptor class B type I (SR-BI) is involved in vitamin E uptake. In the cytosol, fatty acid-binding protein (FABP) and cellular retinol-binding protein (CRBP) transport fatty acids and retinol, respectively. Enzymes in the endoplasmic reticulum, such as ACAT, DGAT, and LRAT, facilitate the esterification of cholesterol, monoacylglycerols, and retinol. These esterified products are incorporated into apolipoprotein B48-containing

chylomicrons (CM) in an MTP-dependent manner and transported to the Golgi apparatus for processing and secretion. Enterocytes also express ATP-binding cassette transporter A1(ABCA1) on the basolateral membrane to facilitate cholesterol efflux. (113)

Niemann-Pick C1 like 1 (NPC1L1) is a protein that plays a vital role in cholesterol uptake, while fatty acid transport protein (FATP) and CD36 are involved in fatty acid transport. Moreover, scavenger receptor class B type 1 (SR-BI) helps in the uptake of vitamin E. In the cytosol, fatty acid-binding protein (FABP) and cellular retinol-binding protein (CRBP) transport fatty acids and retinol, respectively. Cholesterol acyltransferase (ACAT), Diacylglycerol acyltransferase (DGAT), and Lecithin Retinol acyltransferase (LRAT), found in the endoplasmic reticulum membrane, facilitate the process of esterification of cholesterol, monoacylglycerols, and retinol, respectively.

These esterified products are then incorporated into apoB48-containing chylomicrons. Prechylomicrons are transported in specialized vesicles to the Golgi complex for further processing and secretion. Additionally, ATP binding cassette (ABC) transporter A1 facilitates the efflux of cholesterol. (113)

Once inside the enterocyte, the lipids processed and packaged are transported to other body parts where they can be utilized for energy or other essential functions.

5.3. Role of intestinal microbiota in lipid metabolism

The intestinal microbiota, composed of more than 100 000 billion microorganisms, can carry out many processes that cannot be fulfilled by the host, such as energy homeostasis, glucose metabolism, and lipid metabolism, and for this very reason, some are classified as an additional organ. (115,116)

Each individual has around 600 000 bacterial genes and half of them are common to most individuals, while the other half corresponds to de intra-individuality of each human being (117). In this environment, there are three dominant phyla, Fimicutes, Bacteroidetes, and Actinobacteria. (118)

Most of the roles played by the intestinal microbiota can generate metabolites, that work as metabolic substrates and signaling molecules in the host. For instance, bacteria that reside in our colon can aid in the fermentation of available substrates, metabolize food toxins and carcinogens, act as a barrier against pathogenic microorganisms, synthesize vitamins, promote the development and maturation of the intestinal immune system, and interact with epithelial cells, which end up being beneficial for the host's health. However, if the quantity or quality of these metabolites is altered, it can cause perturbations, usually, these alterations occur due to microbial imbalance, also known as dysbiosis, that can be associated with susceptibility to infections, immune disorders, and even with several non-intestinal pathologies such as cardiovascular disease, obesity, diabetes, lever and several brain diseases (119–121)

As mentioned in the previous paragraph, the lipids in our diet can be changed by the gut microbiota, but the lipids can also affect the gut microbiota and its activity. (116)When we consume different types of lipids, we can alter the types of bacteria present in our gut, which can have either beneficial or harmful effects on our health. Certain types of bacteria, such as *Proteobacteria* and *Desulfovibrio* can cause inflammation and harm to the host, while others can be beneficial. (117)

6. Lipid Alterations in Alzheimer's Disease

6.1. Lipid alterations in Alzheimer's Disease

Lipids are important components of various brain structures such as cell membranes. They perform several functions in the brain like transducing cell signaling and storing energy. Additionally, they are responsible for regulating neuronal growth and synaptic plasticity. Lipids also play a role in mediating cell toxicity and apoptosis and help in coping with stress, inflammation, and the aging process. (122) In recent studies, researchers discovered an accumulation of excess lipids in the brain's neurons with tauopathy due to stress or damage. This influx of lipids, forces neurons to pass the excess to the brain's immune cells, called microglia, which will respond with an inflammatory process causing more stress to neurons, worsening the situation and triggering the cycle. (123) In addition to this evidence, alterations in the levels of several lipid species have been reported in AD and potentially linked to pathogenesis, as described below.

6.1.1. Fatty Acids

Fatty acids form the basis of many lipid classes. Elevated levels of their free form, especially in the cerebrospinal fluid of AD brains, along with their metabolic products acyl-carnitines and acyl-CoA, can be neurotoxic and lead to mitochondrial uncoupling and bioenergetic dysfunction. (11,124,125) Unsaturated fatty acids, as ω-3 PUFAs and MUFA are lower in AD patients, along with the DHA levels, while even-chain saturated fatty acids are increased, leading to a reduction of the unsaturated index. (11,125) ω-6 PUFAs are elevated, increasing the pro-inflammatory and pro-oxidative state in the CSF. (126) The unbound form of arachidonic acid, a type of ω-6 PUFA, increases, leading to elevated levels of total phospholipase A2 (PLA2) and calcium-dependent cytosolic PLA2 expression in the cortex and CSF. This affects lipid metabolism, synaptic transmission, as well as the activity of enzymes involved in the formation of amyloid-beta plaques.(11)

6.1.2. Sphingolipids

Glycerophospholipids and Sphingolipids are two types of lipids that are essential to form the cell membrane. The composition and integrity of the membrane, along with neuroinflammation and oxidative stress, are crucial factors in the development of Alzheimer's disease. (127,128) Ceramides, the backbones of Sphingolipids, are the central molecules in the synthesis, recycling and degradation of other sphingolipids. Elevated levels of ceramides can be found early in AD brains, along with a reduction of sphingomyelin. (11,129) These changes are usually associated with upregulated levels of genes involved in ceramide synthesis. Increased amount of ceramides have been implicated in lipid peroxidation, oxidative stress, mitochondrial dysfunction, and neuronal death.(11) In the early stages of AD, ceramide levels, which promote pro-apoptotic signalling, are elevated, while the levels of anti-apoptotic S1P are decreased. (127,130) Ceramide facilitates Aβ production by stabilizing β-secretase, the enzyme responsible for producing Aβ through proteolytic cleavage. Additionally, and as above mentioned, lipid raft regions, serve as anchors for β-secretase and γ-secretase, enzymes directly associated with Aβ production**.** (131)

Sphingomyelins (SMs), the most abundant sphingolipids in the brain, are commonly found in myelin sheaths. (132) Metabolomic assays in AD brains have indicated that higher concentrations of SMs are associated with the severity of AD pathology and an increased risk of abnormal cognition. SMs play a crucial role as components of lipid rafts, acting as γ-secretase inhibitors, and decreasing the synthesis of Aβ40 and Aβ42 peptides, which are associated with AD. (14,133)

Sulfatides, have also been implicated in AD. Studies have shown that sulfatide levels are lower in both gray and white matters of the cerebral cortex during the prodromal and early stages of AD. (134) These reductions in sphingolipid levels have been linked to myelin degeneration and the loss of white matter integrity in the AD brain. (135)

6.1.3. Glycerophospholipids

Glycerophospholipids play a crucial role in the pathogenesis of Alzheimer's disease. Studies have reported decreased levels of phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylinositol (PI) in individuals with AD. (136) The composition of these phospholipids influences the biophysical properties of the membrane, such as, fluidity, charge, and thickness, which directly affects Aβ binding, permeation, and aggregation.(137,138) For example, disrupting PE, which causes an intrinsic negative curvature of the membrane, can prevent Aβ from binding to the membrane and block its toxicity. (131,139)

Moreover, PLA2, an enzyme that hydrolyzes fatty acids from membrane phospholipids, and its product, arachidonic acid AA, mediate Aβ-induced excitotoxicity in AD. It is suggested that this mechanism contributes to the learning and memory deficits observed in AD mouse models. Overall, changes in phospholipid composition and the activity of related enzymes significantly impact the progression of Alzheimer's disease**.** (131,140)

6.1.4. Cholesterol

Cholesterol is known to play a crucial role in AD, as it has an impact on the two main factors that contribute to the disease - Aβ plaque and tau accumulation. The ApoE4 allele has been linked to higher expression of genes involved in cholesterol production and abnormal functioning of genes responsible for transporting cholesterol in oligodendrocytes. This may explain the abnormal accumulation of cholesterol in oligodendrocytes, leading to reduced production of healthy myelin sheaths around axons, affecting the functioning of astrocytes and microglia, ultimately promoting AD pathogenesis. (141,142) Mechanistic studies have shown that the ApoE4 allele directly dysregulates cholesterol pathways in various cell types, contributing to the pathogenesis of AD. Specifically, ApoE4 impairs myelination in oligodendrocytes, causes astrocyte and microglia malfunction, and promotes the accumulation of cholesterol in lysosomes of astrocytes. (142–144) This results in increased expression of cholesterol-manufacturing genes and dysregulated cholesterol-transporting genes, leading to abnormal cholesterol buildup. (131,141) Elevated levels of cholesterol have a significant impact on the processing of APP through various pathways. Cholesterol plays a role in regulating all types of APP proteolytic secretases, including α-, β-, and γ-secretase. Additionally, cholesterol is involved in multiple aspects of Aβ metabolism, such as fibrillation, transportation, degradation, and clearance processes. (141)

6.1.5. Lipid Droplets

Besides alterations in specific lipid species, Alzheimer’s Disease can also be characterized by the presence of an increased number of lipid droplets (LD), an organelle that works as a storage of neutral lipids, increasing p-tau levels. Neuronal hyperactivity alone can induce LDs accumulation in astrocytes and accelerate AD pathologies. In microglia, LDs accumulation has been considered to represent a dysfunctional and pro-inflammatory state in aging brains. Besides being involved in the higher expression of cholesterol, in the absence of neurons, ApoE4 glial cells accumulate more LDs than other APOE variants. (142,145)

Cholesterol inclusion in LDs has been shown to significantly increase p-tau levels, with the ability to be reversed by inhibiting the cholesterol synthesis pathway. Additionally, it has been demonstrated that neuronal hyperactivity alone can induce LDs accumulation in astrocytes and

accelerate AD pathologies. (145) In microglia, LDs accumulation has been firmly linked to a dysfunctional and pro-inflammatory state in aging brains. (146) Furthermore, research indicates that ApoE4-induced LDs accumulation weakens microglial responsiveness to neuronal activity. However, it's important to note that LDs accumulation may also serve as an adaptive response to neurotoxicity, as blocking glial LDs formation has been associated with worsened neurodegeneration. As a result, the debate over whether LDs are detrimental or beneficial in AD remains inconclusive.(131,144)

6.2. Mechanisms contributing to lipid dysregulation and their implication in Alzheimer's Pathogenesis

Numerous studies have identified that lipid-related genes are amongst the strongest risk factors for Alzheimer's disease. These genes include Apolipoprotein E (ApoE), Apolipoprotein J (ApoJ), and ABC A7. High levels of low-density lipoprotein-cholesterol and Apolipoprotein B in the blood are significantly linked to an increased risk of early-onset AD. (122,144)

ApoE4, which is a genetic variant of ApoE, affects sphingolipid metabolism and lipid droplet storage, contributing to the progression of AD. ApoJ, on the other hand, plays a direct role in lipid transport and metabolism, and can also bind to Aβ oligomers. This interference with Aβ aggregation can further induce neurotoxicity with excess amounts of Aβ. Additionally, ApoJ can promote tau pathology by enhancing tau aggregates. (122,147)

Additionally, ApoJ is involved in lipid transport and metabolism and can bind to Aβ oligomers, interfering with their aggregation and thus exacerbating neurotoxicity. (131,148) The ABCA7 gene, with its various splicing isoforms and methylation levels, is strongly associated with AD. Functionally, ABCA7 mediates phagocytosis and immune responses, potentially contributing to AD development. Collectively, these cholesterol-related mechanisms highlight the complex interplay between lipid metabolism and Alzheimer's disease pathology (79,131,149,150)

7. Diagnosis and Available Therapies

7.1. Current diagnostic methods for Alzheimer's disease

Alzheimer's diagnosis can usually be conducted through physical and neurological examinations, which may include testing reflexes, muscle tone and strength, mobility, sensory perception, coordination, and balance. Additionally, imaging techniques and biomarkers obtained through urine, plasma, serum, or cerebrospinal fluid can provide information about grey matter content, white matter differences, the presence of Amyloid, and Positron Emission Tomography (PET) biomarkers indicative of brain disorders. (151,152)

Table 7.1 Current diagnostic methods for Alzheimer's disease

Diagnostic method	Description	References
Positron Emission Tomography (PET)	This technique is a crucial tool for diagnosing AD. It can analyse amyloid proportions in the brain to detect the presence of amyloid plaques, which are a core neuropathologic feature of the disease. PET uses a radioactive tracer to evaluate the metabolic activity in different brain areas, giving information on how the brain reacts to different stimuli. Additionally, it allows for the analysis of cholesterol levels, and measurement of glucose levels in various brain parts.	(152–154)

Structural Magnetic Resonance Imaging (MRI)	MRI provides a detailed anatomical view of the brain, allowing for structure analysis, cortical thickness measurement, voxel-based analysis, longitudinal analysis, and anatomical morphology. It enables the observation of volume changes in characteristic locations typical of AD.	(152,155)
Cerebrospinal Fluid (CSF)	This exam is used to identify the differences between the proportion of Aβ protein in patients with AD and healthy individuals. It is made by examining the changes in Aβ40, and Aβ42, found in the brain region along with phosphorylated tau (p-tau) and tau protein total (t-tau)	(152,156)
APOE4 Detection	Some regions of the human body can be influenced by genetics, and the neuronal region is one of them. The allele E4 of the Apo lipoprotein E in the brain, as referred to previously, can lead to the development of Alzheimer's symptoms, by limiting the production of amyloid in the brain. It can also work as a genetic biomarker, becoming crucial to diagnose AD patients.	(152,157)
Fluid Attenuated Inversion Recovery (FLAIR)	This diagnostic method gives us a flare image, which provides information about an unwanted lesion in the brain or a lesion which suppresses CSF's role in the brain. It also gives information about the white matter remaining in the different parts of the brain affected.	(152,158)
Diffusion Tensor Imaging (DTI)	This technique uses isotropic diffusion to assess the brain's axonal (white matter) structure, by determining the diffusivity of water molecules in tissue, it can identify the fibre bundles gathered in the affected regions of the brain. This is only possible since, in AD, the water molecules stagger communication between neurons and do not follow regularly in the brain.	(152,159)
Electroencephalography (EEG)	EEG measures brainwaves, which are typically displayed in a regular pattern composed of 5 bands of waves. However, the power spectrum, complexity, and synchronization characteristics of EEG waveforms show a distinct deviation from normal in elderly individuals. This deviation is characterized by higher θ oscillation spectral power and lower α oscillation spectral power.	(160,161)

7.2. Available therapeutic options

The latest treatment guideline for AD is divided into three disease states: mild, moderate, and severe. For these three states, the use of ChEIs is indicated, however, memantine can be added for moderate to severe disease states. (162)

Table 7.2 Available therapeutic options

Therapeutic options	Description	References
Cholinesterase inhibitors	Molecules such as Donepezil, Galantamine and Rivastigmine are indicated in AD's treatment. Cholinesterase inhibitors (ChEIs) work by restoring the cholinergic pathway by binding, and inhibiting, acetylcholinesterase (AChE), promoting the increasing of the levels of acetylcholine at the synapse and presumably prolonging its physiological effect. With these molecules, there is a level of improvement that slows down the decline expected over 6 months. Despite this fact, it will reach a point in severe AD, where the use of ChEI will stop to	(162–165)

	present benefits, however, it's still unclear at what point of the disease this medication should be withdrawn. However, when used, ChEIs are generally well tolerated despite common gastrointestinal effects such as nausea and vomiting, which can lead to treatment discontinuation.	
N-Methyl-D-aspartate receptor antagonist (NMDA antagonist)	Memantine prevents the excess of downstream calcium influx and oxidative stress, by blocking the effects of excessive glutamate stimulation at the NMDA receptor. This unusual glutamate accumulation results from an inefficient removal mechanism at the synaptic cleft, resulting in overactivation of the NMDA receptor, leading to chronic excitotoxicity responsible for neuronal loss and cognitive impairment. This molecule presents more effect in moderate to severe AD when compared to its use in mild to moderate.	(162,163,165,166)

7.2.1. Limitations

Treatment for AD should be initiated at the time of diagnosis, and the progression of the disease should be monitored. However, current therapies only slow down the progression of symptoms and do not slow the disease progression or prevent its symptoms or appearance in those at high risk, becoming less and less effective as the disease progresses. (167–169)

8. Future Perspectives and Potential Therapies

8.1. Potential therapeutic strategies targeting lipid metabolism

Abnormal lipid levels can directly accelerate AD progression by encouraging the deposition of Aβ and tau protein tangles. Indirectly, abnormal lipids can increase the burden on brain vasculature, induce insulin resistance, and affect the structure of neuronal cell membranes. (170)

That said, lipid dyshomeostasis may be an initiation mechanism of the disease, given the intimate and strong mechanistic connections among Aβ, ApoE and lipid trafficking. (11)

However, there are some potential AD therapies targeting lipid metabolism under study.

8.1.1. Dietary Modifications

As mentioned earlier, some lipids are changed in AD patients, leading to several studies that have identified certain lipids that can be used in dietary supplements to alleviate AD symptoms. The main lipids include omega-3 fatty acids (DHA, EPA), choline-containing lipids, cholesterol, and lipids with antioxidant properties (CoQ10, Vitamin K). More research focuses on DHA, with recent studies indicating that the most effective way to deliver DHA to the brain is with the help of Msf2a Lysophosphatidylcholine (LPC) receptors. (171,172)

8.1.2. Lipid Transport into the Brain

Several lipoproteins and their respective receptors that bypass the BBB to deliver lipids into the brain are linked to AD pathology, since AD brains have increased BBB permeability and decreased DHA levels. However, some lipids have protective effects, for example, HDL has protective properties by improving Aβ clearance, delaying Aβ fibrilization, suppressing vascular inflammation, and inducing endothelial nitric oxide production. (172,173)

8.1.3. Cholesterol Metabolism

Cholesterol metabolism is altered in AD, so the modulation of its metabolism may be beneficial for these patients. The modifications can be done during its consumption, at the level of its biosynthesis and during its transport into the brain.

Gene therapy that targets cholesterol 24-hydroxylase has been found to reduce amyloid pathology in mouse models of Alzheimer's disease. (174) Studies suggest that blocking the conversion of cholesterol to cholesterol esters could positively affect Alzheimer's disease since it might decrease its accumulation in lysosomes of astrocytes (175). Research has proposed that cholesterol metabolites could be valuable targets for different treatments or prevention of Alzheimer's disease, since high cholesterol enhances the activity of β- and γ-secretases, leading to an accumulation of Aβ, cholesterol-lowering therapies could be quite beneficial (176). Additionally, in a rodent model of Alzheimer's disease, treatment with the anti-inflammatory steroid atorvastatin has been shown to regulate the inflammatory process mediated by toll-like receptor 4 (TLR4) signaling, improving cognitive deficits.(172)

8.1.4. Lipolytic Enzymes

Multiple lipolytic enzymes are affected in AD. PLA2 is connected to amyloid plaques, and decreasing its activity and expression improves AD symptoms. There is an increase in PLA2 activity in the CSF of AD patients, which is accompanied by a rise in LPC. LPC is known to disrupt the blood-brain barrier (BBB), and changes in PLA2 are associated with inflammation. (177)

The connection between PLA2 and AD pathology suggests that inhibiting PLA2 activity or expression may be an effective way to prevent AD. However, isoform-specific inhibitors are needed to avoid the toxicity associated with non-selective inhibitors. In addition to PLA2, the expression and activities of phospholipase D (PLD) and phospholipase C (PLC) are also associated with AD pathology. These enzymes, which are linked to neurite growth and signaling, offer other potential avenues for exploring treatments for AD. (172)

8.1.5. Lipid Oxidation Inhibitors

The brain's most crucial fatty acid, DHA, is a polyunsaturated fatty acid that is highly susceptible to oxidative damage. While HDL protects against oxidative damage, very low density cholesterol (VLDL) is easily oxidized. Measures that decrease oxidation are expected to slow down the progression of AD. These measures include the use of natural antioxidants, carnosine, lipoic acid, Ginkgo biloba flavonoids, soybean isoflavones, vitamin K, homocysteine, and curcumin. The role of endogenous lipids in oxidative stress can be utilized when there is uncontrolled formation of ROS and RNS or when antioxidants contribute to disease pathology.(172,178–180)

8.2. Evaluation of preclinical and clinical studies investigating lipid-based interventions

Several studies are being developed for Alzheimer’s treatment based on lipid metabolism.

Ongoing research on EPA and DHA is still in its early stages, but it shows promising potential in restoring the integrity of the phospholipid membrane and enhancing the function of neuronal membranes. However, studies in mice showed that low levels of DHA-containing phospholipids were associated with lower levels of soluble Aβ42, higher levels of phosphorylated α-synuclein, and reduced synaptic proteins.(181) There is a study being conducted until 2025 to explore the link between DHA levels in humans and the presence of the ApoE4 gene since the initial findings suggest that in certain cases, DHA supplementation has led to an increase in DHA levels in the CSF. (182)

Certain medications that are commonly used to treat hypercholesterolemia, a condition characterized by high levels of cholesterol in the blood, are currently undergoing research to explore their potential use in the treatment of AD. This development has sparked considerable interest within the medical and scientific communities, as it represents a potential repurposing of existing medications for a different therapeutic application. If successful, this could lead to significant advancements in managing Alzheimer's disease.

Atorvastatin, an inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA), is used to lower peripheral cholesterol, and in the latest years, it was noted to protect against AD. (183). In a study conducted in 2006, 16 middle-aged, cognitively normal adults who had a parent with Alzheimer's disease were enrolled to take atorvastatin for four months. The study showed that atorvastatin had a positive effect on neurovascular response and cerebral blood flow. (184–186)

A larger study on simvastatin, an oral HMG-CoA reductase inhibitor, began in 2009 and is set to run through 2019. The study, conducted at 17 centers throughout Germany, aims to randomize 445 people with both self-reported and measurable memory impairment but preserved function to a two-year course of either 60 mg of simvastatin or a placebo once daily. This study measures the time until participants develop dementia, with "conversion" to dementia defined as an increase in the Clinical Dementia Rating (CDR) score past 0.5. (187) While the previous study has not yet presented its results, another study conducted in Yeast Cells demonstrated that Simvastatin effectively decreased levels of the cellular Aβ42 protein in a dose-dependent manner. (188)

Gemfibrozil, activates the peroxisome proliferator-activated receptor-α (PPARα), a nuclear receptor involved in lipid metabolism. This drug class, the fibrates, has the capacity to reduce triglyceride levels, being prescribed to control cholesterol. Some preclinical studies showed that treating AD mouse models with gemfibrozil, decreased the amyloid plaque accumulation, in the cortex and hippocampus, improving learning and memory in a PPARα-dependent pathway.(189,190) In May 2014, a trial funded by the National Institute on Aging at the University of Kentucky began to assess whether gemfibrozil can safely adjust microRNA-107 levels for the prevention or early-stage treatment of AD. The study included 48 cognitively normal and 24 mildly impaired participants for a one-year period. Changes in CSF Aβ42, p-tau, and p-tau/Aβ42 ratio over time indicated positive trends with the treatment compared to the placebo, but the differences were not statistically significant. (191)

In addition to existing molecules, there have been studies conducted on newly discovered molecules.

CS6253 is an agonist peptide that increases the activity of ABCA1, a transporter that regulates cholesterol efflux from cells. ABCA1 transfers lipids to ApoE, facilitating the clearance of amyloid peptides and slowing down hyperphosphorylation in neurons in the brain.(77,192,193) A Phase 1 safety trial, funded by the National Institutes of Health and the Alzheimer’s Association, began in September 2023 and will last for a year. It is enrolling around 64 healthy adults, with the drug administered by intravenous injection in five single-ascending-dose cohorts ranging from 1 to 10 mg/kg, as well as in two or more multiple-dose groups.(194)

Obiceratip is a cholesteryl ester transfer protein (CETP) inhibitor that prevents the transfer of cholesteryl esters from HDL into other lipoproteins. This action promotes the removal of cholesterol by HDL. (195) By increasing HDL levels, obicetrapib enhances the removal of cholesterol from cells, which may reduce the risk of Alzheimer's disease associated with ApoE4 and aid in clearing Aβ from the brain. However, a recent study found that genetic variants linked to higher HDL levels were actually associated with an increased risk of Alzheimer's disease. (196,197)

Trappsol® Cyclo™ is an intravenous formulation of 2-hydroxypropyl-β-cyclodextrin that sequesters cholesterol, solubilizing it and extracting it from cells. In preclinical studies related to AlD, injections of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) improved spatial learning and memory deficits and reduced amyloid plaque deposition and tau-containing dystrophic neurites in the Tg19959 mouse amyloidosis model. The drug also decreased APP cleavage and increased the expression of genes associated with cholesterol transport and Aβ clearance (198). In other models with impaired autophagy-mediated clearance of Aβ, HP-β-CD restored lysosomal function (199,200). Additionally, HP-β-CD itself sequestered Aβ in vitro, inhibiting peptide aggregation and toxicity (201). According to a press release in June 2020, the drug was deemed safe, and the patient's condition did not worsen. In September 2022, a Phase 2 study began to evaluate the drug's effectiveness in early Alzheimer's disease, running through March 2024.(202)

There have been several studies conducted on Efavvirenz, an FDA-approved anti-retroviral medication used for human immunodeficiency virus infection. These studies found that doses 100 times lower than those used for HIV can promote cholesterol efflux from the brain. (203)

One study discovered that low-dose efavirenz lowers brain cholesterol by activating the enzyme cholesterol 24-hydroxlyase, also known as CYP46A1. (204) This enzyme-mediated modification is the major pathway for eliminating excess cholesterol from the brain. The reduction of cholesterol esters in this system promoted phospho-tau degradation by the proteasome. Additionally, the drug reduced Aβ42 production through a different mechanism involving cholesterol binding to the amyloid precursor protein. In another study, efavirenz was found to promote the uptake of tau seeds into cells by altering the cholesterol makeup of cell membranes. (205) In May 2018, a Phase 1 trial began at two U.S. hospitals to test the target engagement of efavirenz in people with Alzheimer’s disease and mild cognitive impairment or mild dementia. However, the trial ended in January 2022 after enrolling only five patients, partly due to the COVID-19 pandemic. (206)

8.3. Challenges and opportunities in translating lipid-based therapies into clinical practice

Translating lipid-based therapies into clinical practice presents several challenges and opportunities.

As stated earlier, there are numerous potential areas for exploration, including the dysregulation of cholesterol metabolism, alterations in phospholipid membranes, the development of therapies targeting sphingolipids and ceramides to mitigate neuroinflammation, as well as the creation of new drug delivery systems to bypass the blood-brain barrier and novel diagnostic approaches.

Understanding the intricacies of brain metabolism is a complex task due to its partially unknown nature. This complexity makes it challenging to predict how different therapies will interact with the brain and whether they can effectively cross the BBB. Furthermore, AD has a multifactorial etiology, since it can have genetic or non-genetic origins, resulting in a diverse disease background among patients.

9. Conclusion

As the world's population grows older, the incidence of Alzheimer's disease continues to rise, posing significant challenges to global health systems. Since the core of this pathology started being explored, it was suspected that lipids had some role in the development of this disease. Now it is known the significant impact of lipid dysregulation on the onset and progression of this neurodegenerative disorder, as they interact with key AD pathogenic mechanisms such as amyloidogenesis, oxidative stress, bioenergetic deficits, neuroinflammation, and myelin degeneration.

Lipidic metabolism dysregulation is not merely a consequence but a contributing factor to the pathophysiology of AD. Specific lipid alterations, including changes in glycerophospholipids, sphingolipids, and cholesterol levels, have been consistently observed in AD patients. These lipid changes are linked to the formation of amyloid plaques and neurofibrillary tangles, the hallmarks of AD, which exacerbate neuronal damage and cognitive decline.

Genetic factors, particularly the presence of the ApoE4 allele, play a crucial role in lipid metabolism and are associated with an increased risk of developing AD. The ApoE4 allele influences the metabolism of sphingolipids and cholesterol, leading to lipid accumulation in the brain and promoting AD pathogenesis. Additionally, environmental factors such as diet significantly affect lipid metabolism, with diets high in saturated fats and low in omega-3 polyunsaturated fatty acids (PUFAs) contributing to lipid dysregulation and increased AD risk.

Despite the promising potential of lipid-based therapeutic strategies, several challenges need to be addressed. These include the complexity of lipid interactions within the brain, the difficulty of delivering lipid-based therapies across the blood-brain barrier, and the variability in individual responses to treatment. Nevertheless, recent advancements in understanding lipid metabolism in the brain have opened new avenues for developing targeted interventions aimed at restoring lipid homeostasis.

Future research should focus on exploring novel lipid-based therapies, optimizing delivery methods, and identifying biomarkers for early diagnosis and monitoring of disease progression. Additionally, comprehensive clinical trials are necessary to evaluate the efficacy and safety of these therapeutic strategies.

In conclusion, lipid metabolism plays a pivotal role in the pathogenesis of Alzheimer's disease. Understanding the complex relationship between lipid dysregulation and AD pathophysiology is essential for developing effective diagnostic and therapeutic approaches. Continued research in this field holds the promise of improving the quality of life for individuals affected by AD and reducing the societal and economic burden of this devastating disease.

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