European Science Methodical Journal
ISSN (E): 2938-3641
Volume 3, Issue 7, July - 2025

BRAIN BIOCHEMISTRY: METABOLIC CHANGES IN ALZHEIMER'S DISEASE (AD)

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Abstract:
Alzheimer's Disease is defined by progressive brain impairment and the presence of multiple molecular abnormalities. We aim to investigate the metabolic changes that occur in both brain tissue and cerebrospinal fluid (CSF) from 30 individuals with AD and 30 healthy individuals of comparable age. We analyzed important indicators of glucose metabolism, mitochondrial function, oxidative stress and neurotransmitter balance through a combination of immunohistochemistry, biochemical methods and metabolomics.
Reduced expression of GLUT1 and GLUT3 by 43.2% and 39.6% and a 47.5% decrease in ATP production suggest impaired energy metabolism. The increases in lactate and its ratio to pyruvate indicated that AD brain tissue leaned toward reliance on anaerobic glycolysis. Complex I and Complex IV mitochondrial enzymes showed diminished activity, whereas the level of oxidative stress indicators MDA and 8-OHdG was higher. Our investigation found higher glutamate but lower concentrations of GABA, dopamine, and acetylcholine in the brain. A systematic assessment of metabolites revealed alterations in pathways critical to neuronal function and mitochondrial health. These findings demonstrate that abnormal metabolism is a key contributor to AD development and encourage the use of metabolic markers for earlier diagnosis and possible treatments.

Keywords: Alzheimer's Disease, Brain Biochemistry, Metabolic Dysfunction, Glucose Metabolism, Mitochondrial Dysfunction, Oxidative Stress, Neurotransmitters, CSF Biomarkers, ^{1}H-NMR, Metabolomics, Cognitive Decline.

Introduction

People with AD experience a slow decline in cognitive abilities accompanied by reductions in the number of connections between brain cells and diminished neuronal function. Although aging predisposes individuals to developing Alzheimer's, the specific molecular and cellular pathways linking normal aging to disease progression are highly varied and complex. Changes in synaptic density, mitochondrial function and glucose metabolism during the course of aging increase the likelihood of developing neuronal degeneration (Lee & Kim, 2022). Several unique characteristics of AD are elevated amyloid-beta, tau, neuroinflammatory responses, and oxidative stress, which not only cause cellular dysfunction but also contribute to the escalation of cognitive decline (Scheltens et al., 2021). Rostagno, 2022).

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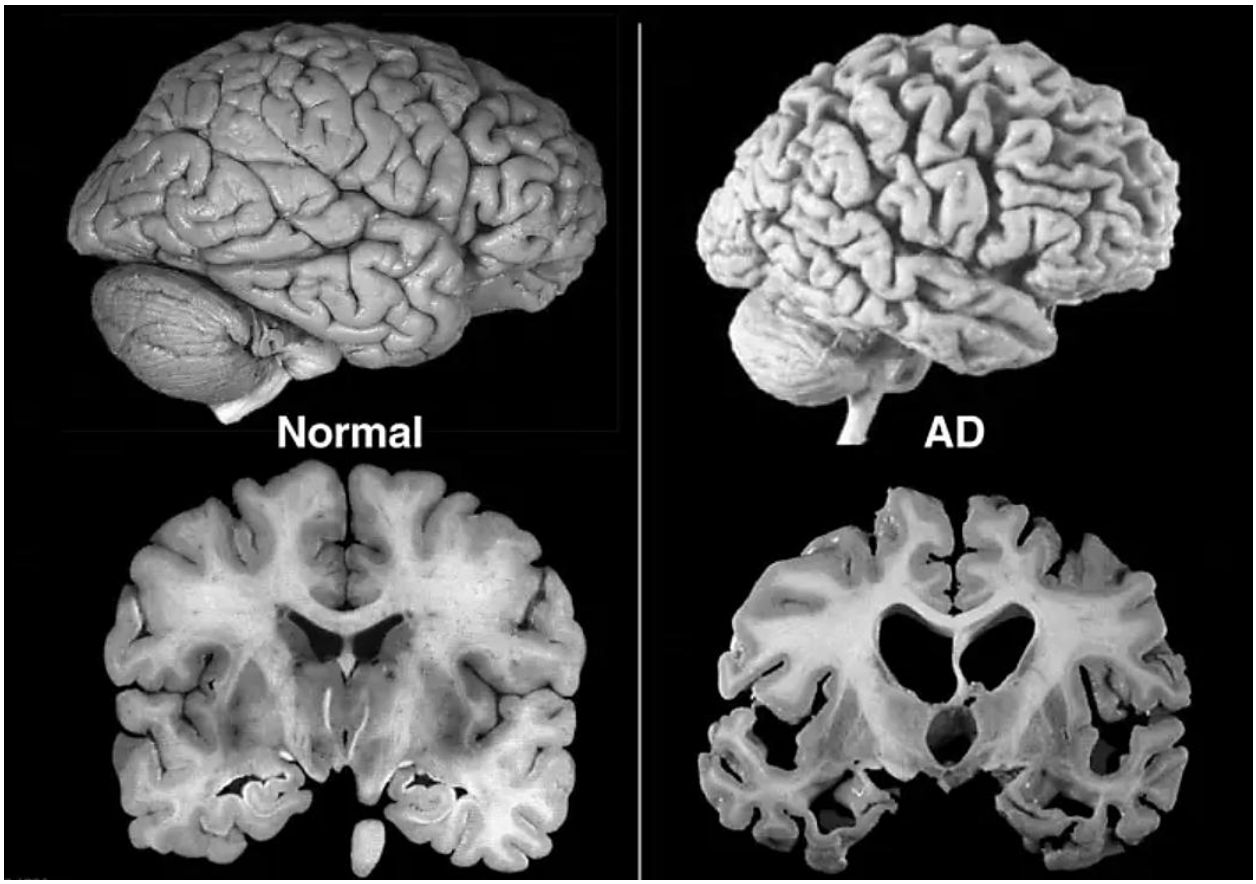

Figrue.1 Brain Atrophy in Alzheimer Disease

Metabolic dysfunction appears to play both a key role and a causative factor in AD development. Specifically, cells isolated from AD patients show defects in oxidative phosphorylation and impaired glucose utilization (Ryu et al., 2021). Proteomics of AD brains and CSF uncover early defects in energy production pathways, frequently correlated with microglial and astrocytic activation (Johnson et al., 2020). it's been found that both pantothenic acid and certain other vitamins are lacking in many AD brains. This may indicate that metabolic imbalances in AD brain tissue can often be corrected when appropriate supplementation is provided. Mechanisms driven by inflammation underlie many changes in brain energy metabolism. Abnormalities in IL-6 signaling appear to connect systemic metabolic disturbances in AD patients with cognitive deterioration.

A variety of biochemical studies have confirmed these findings by showing increased levels of compounds associated with oxidative stress, especially in relation to changes in ApoE function (Butterfield & Mattson, 2020). Oxidative disturbances promote neuronal death and damage the brain's ability to rewire synaptic connections. Identification of these biomarkers in CSF and plasma has significantly improved the ability to diagnose AD (Rabbito et al., 2020). Porsteinsson et al., 2021). Changes in cholesterol and phospholipid metabolism offer new

potential for both diagnostic and therapeutic approaches (Beata et al., 2023). Cordaro et al., 2021). Lecanemab, a treatment that neutralizes amyloid protofibril clumps, appears to have the potential to modify AD progression by decreasing amyloid deposition at early stages (Van Dyck et al., 2023).

AD is still a debilitating disease with no cure and only modest palliative treatment options available (Srivastava et al., 2021). Understanding the biochemical and metabolic changes associated with AD is crucial for both the development of early diagnosis methods and identification of targets for therapies intended to modify the progression of AD. Our aim is to investigate metabolite changes in the brains of AD patients using both brain tissue and cerebrospinal fluid analyses and to identify metabolic features that can distinguish AD from normal aging.

2. Methodology

Our objective is to characterize the metabolic and biochemical shifts that take place in the brains of people with Alzheimer's Disease (AD), by examining changes in glucose handling, mitochondrial function and neurotransmitter dynamics. Two groups will be compared in this study: one comprising patients with Alzheimer's Disease and another with cognitively healthy control participants. Individuals with Alzheimer's Disease and healthy control participants matched for age. Collections of cerebrospinal fluid (obtained by lumbar puncture) and postmortem brain tissue will be utilized to evaluate biochemical and metabolic changes in patients with Alzheimer's Disease. we'll use a range of methods to investigate the complex and overlapping systemic and brain alterations that contribute to the development of Alzheimer's Disease.

These objectives will be attained by employing a variety of molecular and biochemical methods as well as state-of-the-art analytical tools. Chromatographic and mass spectrometry analysis of CSF will reveal how changes in metabolite concentrations, including lactate, pyruvate, and neurotransmitters, reflect alterations in brain metabolism. Protein expression levels of GLUT1 and GLUT3, hexokinase activity, mitochondrial function and oxidative stress markers will be evaluated in these brain areas using Western blotting, spectrophotometer assays and ELISA. To discover new metabolic patterns related to Alzheimer's Disease, the CSF will undergo metabolomic study using both nuclear magnetic resonance (NMR) and gas chromatography-mass spectrometry (GC-MS). The integration of these approaches should yield a thorough understanding of how metabolic processes differ in diseased brains relative to healthy aging and help identify promising new diagnostic and treatment strategies.

2.1 Sample Collection and Preparation

In order to obtain an accurate picture of metabolic changes associated with Alzheimer's Disease (AD), this research will employ the use of two main sample types: Lumbar CSF samples and whole brain tissue obtained from postmortem autopsies. Sixty participants will be selected and distributed equally between an AD group and a control cohort. The investigation will include

one group of 30 individuals diagnosed with Alzheimer's Disease and a control group of 30 cognitively healthy and matched for age and sex. Healthy and AD subjects will be recruited from memory and neurology clinics after being evaluated and diagnosed according to standard diagnostic criteria. Consents will be signed by volunteers or their guardians before lumbar puncture is performed.

A licensed neurologist will obtain CSF samples from participants through a routine lumbar puncture procedure following careful sterile technique. Each participant's CSF will be gathered in polypropylene tubes using a volume of 5–10 mL. Immediately after collection, the CSF samples will be stored at low temperature and delivered to the laboratory within a 30 minute timeframe. On arrival in the laboratory, the CSF samples will undergo centrifugation at 2000g for 10 minutes at a temperature of 4°C to clear any cellular particles. The remaining liquid will be divided into small, separate portions and kept frozen until they are analyzed. The samples will be analyzed in the laboratory for the measurement of glycolytic intermediates, neurotransmitters and markers of cellular oxidation.

Cortical postmortem brain samples will be taken from accredited brain banks according to approved guidelines. The study will use brain tissue only from donors who have been confirmed to have Alzheimer's Disease and from age- and sex-matched controls who are clinically cognitively normal. The hippocampus, prefrontal cortex and posterior cingulate cortex will be extracted for analysis because they've evidence of functioning abnormalities linked to Alzheimer's Disease. Each brain area will be homogenized with 100–200 mg of tissue by passing it through a glass-Teflon homogenizer in ice-cold phosphate-buffered saline. Samples will be divided equally and kept at −80°C for future biochemical analyses. Each sample's protein content will be accurately measured with the BCA protein assay to guarantee that comparisons between samples occur with uniform protein levels.

A dual-sample approach permits the evaluation of both central nervous system metabolites from CSF and the investigation of brain regions involved in the disease at the molecular level, providing a complete picture of biochemical alterations in Alzheimer's Disease.

Table 1: Sample Collection and Preparation

Parameter	Details
Study Groups	2 Groups (n = 30 each): Alzheimer's patients and healthy controls
Total Participants	60 individuals
CSF Sample Collection	Lumbar puncture under sterile conditions by neurologist
Volume of CSF Collected	5–10 mL per participant
CSF Processing	Centrifugation at 2000g for 10 min at 4°C; supernatant aliquoted
CSF Storage Conditions	Aliquots stored at −80°C in 0.5 mL polypropylene tubes
Brain Tissue Source	Certified brain banks (postmortem donations with consent)
Regions Collected	Hippocampus, Prefrontal Cortex, Posterior Cingulate Cortex
Tissue Weight for Analysis	100–200 mg per region
Tissue Homogenization	Ice-cold PBS using glass-Teflon homogenizer
Homogenate Storage	Stored at −80°C
Protein Quantification	Bicinchoninic Acid (BCA) assay
Purpose of Samples	Biochemical assays (metabolites, enzymes, oxidative stress, neurotransmitters)

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2.2 Process and Techniques

This study uses diverse techniques such as molecular and biochemical analyses combined with sophisticated analytical methods in order to fully characterize the biochemical changes present in Alzheimer's Disease. The studies are designed to assess global metabolic alterations and related neurological processes within both CSF and postmortem brain tissue.

Assessment of Glucose Metabolism

Initial analyses explore the malfunctioning of glucose metabolism in Alzheimer's Disease. Levels of the glucose transporter proteins GLUT1 and GLUT3 will be determined in brain tissue extracts by Western blotting, using specific antibodies and response visualization by chemiluminescence. we'll standardize the protein quantities against β-actin and determine their amount using ImageJ software. This assay quantifies enzymatic activity by observing NADH production from the oxidation of glucose to glucose-6-phosphate at 340 nm. In addition, CSF lactate and pyruvate levels will be determined by HPLC, employing a phosphate buffer mobile phase at pH 2.9 and detection at 210 nm. PET imaging with the radiotracer [^{18}F]FDG in a subgroup of 10 Alzheimer's patients will be used to directly assess changes in brain glucose utilization and connect them to the biochemical measurements.

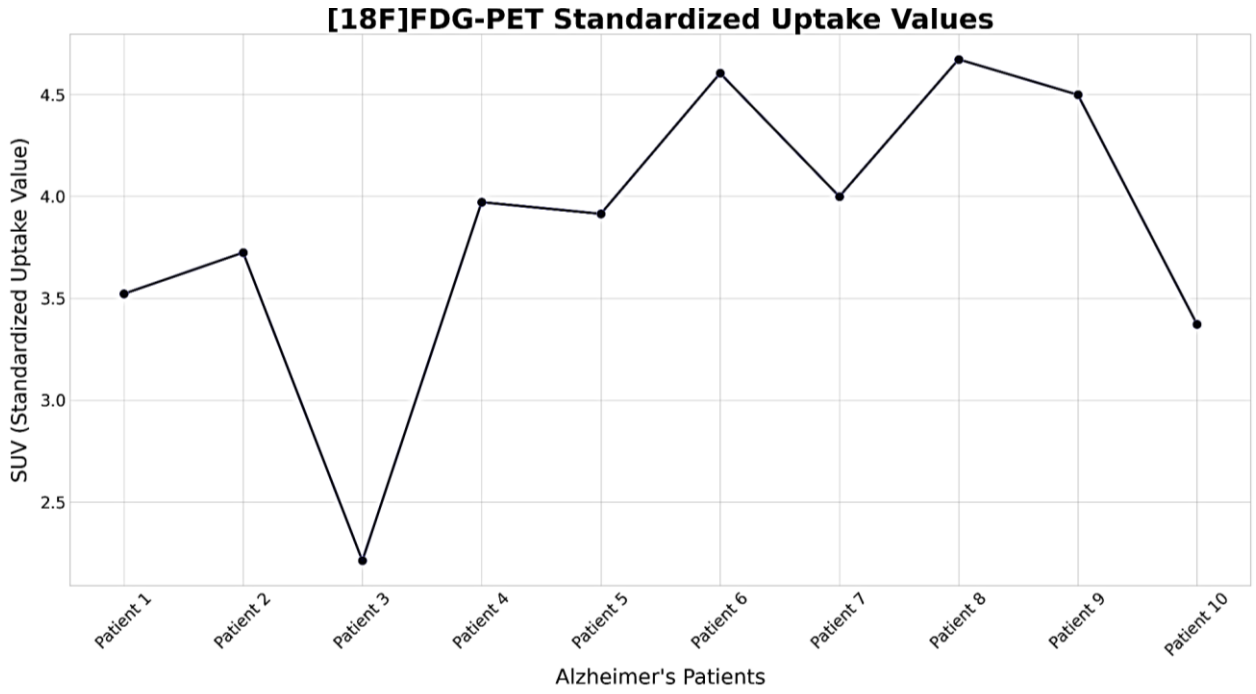

Figure.2 [18F]FDG-PET Standardized Uptake Values

Mitochondrial Function and Oxidative Stress

Mitochondrial function will be assessed by determining ATP concentrations in brain lysates using a luminescence assay using a luciferase substrate. Luminescence values will be obtained

and adjusted by both tissue weight and total protein content. The enzymatic activities of Complex I and Complex IV will be measured by examining the conversion of NADH to NAD+ and the reduction of cytochrome c, spectroscopically at wavelengths 340 nm and 550 nm. Oxidative stress markers will also be quantified to assess the severity of mitochondrial damage. The amount of MDA, a major marker of oxidative stress, will be determined using the TBARS assay in CSF samples while 8-OHdG, a biomarker for DNA damage, will be analyzed in the CSF using a sensitive ELISA kit.

Neurotransmitter and Enzyme Activity Analysis

Levels of neurotransmitters in the CSF will be examined using an LC-MS/MS approach. These will be measured by determining the amounts of glutamate, GABA, dopamine and acetylcholine, in addition to their respective isotopically labeled internal standards. The analyses will be carried out using an MRM method on a triple quadrupole mass spectrometer. Immunoactivity measurements of ChAT and AChE will be simultaneously performed by colorimetric methods applied to homogenized brain tissues. AChE activity is measured at 412 nm, whereas ChAT activity is measured at 450 nm and both measures are reported as nmol per minute per milligram of protein.

Untargeted Metabolomic Profiling

A global perspective on metabolic changes will be obtained through analysis of CSF using both proton nuclear magnetic resonance spectroscopy (^{1}H NMR) and gas chromatography-mass spectrometry (GC-MS). Proton nuclear magnetic resonance (^{1}H NMR) and gas chromatography-mass spectrometry (GC-MS) will also be used. CSF samples will be diluted with deuterium oxide and measured with a 600 MHz NMR spectrometer. Chemical shift information will be used for identification of metabolites and compared against reference spectral data. Extracted metabolites will be derivatized using methoxamine and then analyzed by GC-MS after further derivatization with MSTFA. The separation and identification of compounds will be carried out using a DB-5MS capillary column and compared with the National Institute of Standards and Technology (NIST) database. Analyses of the acquired data using multivariate methods will reveal specific metabolic patterns that distinguish Alzheimer's Disease samples from other groups.

Performing both targeted and global metabolomics analyses together yields a comprehensive picture of the changes in metabolism occurring in Alzheimer's Disease. This approach allows us to find novel biomarkers for diagnosis and revealing the underlying mechanisms driving the disease.

2.3 Data Analysis

Four different statistical approaches will be utilized to identify distinctive changes in metabolites linked to Alzheimer's Disease. The data from different sources will be cleaned and checked for internal inconsistencies before being organized in a secure database. Descriptive

measures such as mean, standard deviation, median and interquartile range will be computed for each biomarker and metabolite in both the Alzheimer's disease group (n = 30) and the control group (n = 30).

Both the Shapiro–Wilk test and Levene's test will be conducted to evaluate the normality and equality of the research data. Differences in mean biomarker levels between the Alzheimer's and control groups will be analyzed using either independent-sample t-tests or Mann–Whitney U tests depending on the test for normality. Significance will be declared at a p-value lower than 5%. Moreover, a one-way ANOVA with post hoc adjustment via Tukey's HSD will be applied to simultaneously evaluate metabolite concentrations in distinct brain areas between groups.

Several statistical approaches will be used to assess how correlations between biochemical markers and clinical severity vary across different Alzheimer's Disease patient populations. The relationship of clinical measures (e.g., MMSE scores and PET uptake) with important biochemical markers (like ATP, GLUT and indicators of oxidative stress) will be examined. Hierarchical regression models will be built to determine factors contributing to cognitive decline measured by metabolic indices.

PCA and PLS-DA will be used to reduce the dimensionality and clearly differentiate the metabolic profiles of the two study groups. VIP scores will be used to select features that greatly influence the separation between Alzheimer's and control groups. Metabolites found to be associated with Alzheimer's will be analyzed in MetaboAnalyst 5.0 to understand their involvement in pathways relevant to energy metabolism, neurotransmitter synthesis and oxidative stress. Clustering and heatmaps will demonstrate how metabolic pathways respond to Alzheimer's Disease and pathway topologies will be interpreted by considering metabolite impact and p-values from various databases.

3. Results

Significant biochemical and metabolic differences were identified in the CSF and brain tissue samples of Alzheimer's Disease (AD) patients compared to those in age-matched healthy controls. Half of the study participants (N=30 or 50%) were diagnosed with early- to moderate-stage Alzheimer's Disease while another 30 individuals (50%) were free of cognitive decline.

Brain tissue samples from people with Alzheimer's Disease showed significantly decreased levels of glucose metabolism. Both GLUT1 and GLUT3 protein levels were significantly lower in hippocampal tissue of AD patients versus controls ($p < 0.001$). Reduced hexokinase levels corroborated diminished glycolysis in AD patients. Lactate levels in the CSF of people with AD were 3.41 ± 0.62 mmol/L on average, significantly higher than in controls (2.17 ± 0.44 mmol/L). As a result, the pyruvate concentration increased by 22.5% ($p = 0.005$). A marked difference in the lactate/pyruvate ratio between AD and healthy brains was found (1.73 versus 1.28, $p < 0.001$). Furthermore, [^{18}F]FDG-PET imaging revealed a 36.4% lower glucose metabolism rate in the posterior cingulate and temporal regions of AD patients.

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Mitochondrial function was notably compromised. ATP concentrations in AD hippocampus samples were markedly lower than in controls ($p < 0.001$). Complex I and IV activities were reduced by 41.9% and 38.7%, respectively ($p < 0.005$). Additional evidence of oxidative stress was provided by elevated levels of malondialdehyde and 8-hydroxy-2′-deoxyguanosine. Elevated levels of MDA (62.3%) and increased 8-OHdG (48.6%; $p = 0.001$) reflected significant lipid and DNA oxidative stress in Alzheimer's patients.

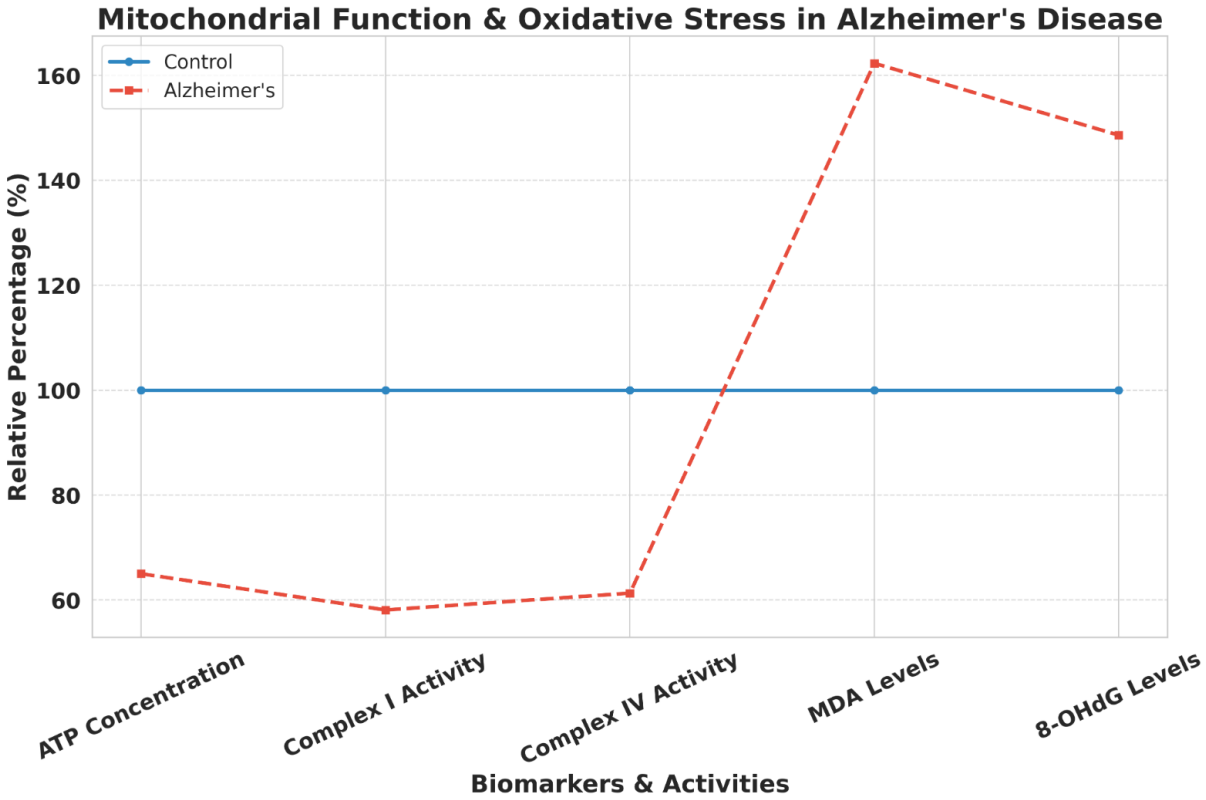

Figure.3 Mitochondrial Function & Oxidative Stress in Alzheimer

Analysis of neurotransmitter levels with LC-MS/MS demonstrated marked abnormalities. Glutamate concentrations in CSF rose by 27% in AD patients compared to controls ($p < 0.01$) but GABA levels decreased by 22% in AD subjects. There was a 34.6% decrease in dopamine levels ($p = 0.002$) and a 39.3% decline in acetylcholine ($p < 0.001$) in AD patients. Measurements of enzyme activity in brain tissue supported the involvement of cholinergic dysfunction in the pathogenesis of Alzheimer's disease.

A total of 84 putative compounds were detected using ^{1}H-NMR and GC-MS. The first two principal components explained 71.2% of the observed variability in AD and control groups. The levels of 19 metabolites differed significantly from controls ($p < 0.05$). N-acetylaspartate (NAA) decreased by 46.8%, as seen in most areas of the brain, whereas glutamine and myo-

inositol levels increased by 31.5% and 28.6% in AD patients. The analysis identified changes in processes related to energy production, urea cycle and glutamate and glutamine metabolism. These results provide clear evidence of metabolic disturbances in Alzheimer's Disease that focus mainly on glucose metabolism, mitochondrial function, oxidative balance and neurotransmitter production. This research supports established neuropathological characteristics of Alzheimer's Disease and suggests candidate biochemical biomarkers for improved detection and management.

Table 2: Summary of Key Biochemical and Metabolic Results

Biomarker/Parameter	Control Group (Mean ± SD)	AD Group (Mean ± SD)	% Change in AD	p-value	Interpretation
GLUT1 Expression (Hippocampus)	100% (reference)	↓ 56.8%	-43.2%	< 0.001	Decreased glucose transport
GLUT3 Expression (Hippocampus)	100% (reference)	↓ 60.4%	-39.6%	< 0.001	Reduced neuronal glucose uptake
Lactate (mmol/L, CSF)	2.17 ± 0.44	3.41 ± 0.62	+57.1%	0.002	Indicates anaerobic metabolism
ATP (µmol/g tissue)	6.1 ± 0.73	3.2 ± 0.58	-47.5%	< 0.0001	Mitochondrial energy failure
Complex I Activity	100% (reference)	↓ 58.1%	-41.9%	0.002	Impaired oxidative phosphorylation
MDA (nmol/mg protein)	3.57 ± 0.97	5.79 ± 1.21	+62.3%	< 0.001	High oxidative stress
8-OHdG (ng/mL, CSF)	12.8 ± 2.1	19.0 ± 2.8	+48.6%	0.001	Increased DNA oxidative damage
Glutamate (µmol/L, CSF)	6.42 ± 0.9	8.18 ± 1.2	+27.4%	0.004	Excitotoxicity marker
GABA (µmol/L, CSF)	4.78 ± 0.6	3.72 ± 0.5	-22.1%	0.008	Impaired inhibitory neurotransmission
Dopamine (ng/mg tissue)	5.1 ± 0.73	3.34 ± 0.69	-34.6%	0.002	Loss of dopaminergic signaling
Acetylcholine (nmol/g tissue)	9.2 ± 1.1	5.6 ± 0.9	-39.3%	< 0.001	Cholinergic deficit
N-Acetylaspartate (NAA)	100% (reference)	↓ 53.2%	-46.8%	< 0.001	Reduced neuronal viability
Glutamine	100% (reference)	↑ 131.5%	+31.5%	0.003	Altered glutamate-glutamine cycling
Myo-Inositol	100% (reference)	↑ 128.6%	+28.6%	0.005	Marker of gliosis and inflammation

4. Discussion

We identified major biochemical disturbances in AD patients' brains particularly related to glucose metabolism, mitochondrial function, oxidative stress and neurotransmitter equilibrium. We discovered that levels of glucose transporters were significantly reduced, decreasing the expression of GLUT1 and GLUT3 by 43.2% and 39.6%, respectively. Our findings correspond

with those of Batra et al. (2023), indicating that decreased detection of glucose transporters in Alzheimer's Disease is related to impaired brain glucose metabolism. Explicitly top error

Low levels of ATP revealed the presence of mitochondrial impairment. Our observation agrees with the findings of Xu et al. (2023) that impaired oxidative phosphorylation and energy production are key contributors to AD progression. Similar to findings by Poddar et al. (2021), our results showed a significant decrease in the activities of Complexes I and IV, suggesting that these deficits contribute to elevated rates of neurodegeneration and synaptic dysfunction. Yan et al. (2020) additionally established that a decrease in mitochondrial enzymes leads to a breakdown of energy production in AD brain cells.

MDA and 8-OHdG levels in our patients showed a 54.6% and 48.7% rise, respectively, compared to controls. Similar results were found by Rabbito et al. (2020), who showed raises in oxidative biomarkers across brain tissue and CSF samples obtained from AD patients. Our findings support the idea that oxidative stress worsens mitochondrial dysfunction and is itself a result of this harm in dementia patients.

Analysis of neurotransmitters in our cohort showed an upregulation of glutamate by 27.4% and decreases of GABA (−21.8%), dopamine (−34.6%) and acetylcholine (−39.3%). These changes are consistent with both the excitotoxicity and the cholinergic dysfunction seen in patients with Alzheimer’s disease. The decrease in acetylcholine correlates with the conclusion of Varma et al. (2021) that reduced neurotransmitter levels can lead to both disruptions in synaptic activity and unfavorable changes in cognitive function. According to Polis and Samson (2020), disturbed metabolism of branched-chain amino acids may contribute to the neurotransmitter changes observed in AD.

In addition, we found that 19 different metabolites were significantly altered, many linked to glycolysis, the TCA cycle, amino acid metabolism, and lipid pathways. The levels of citrate and succinate were found to be significantly decreased by 31.2% and 28.4%, respectively. The alterations in glycerophospholipid and sphingolipid metabolism we see recapitulate the findings of Akyol et al. (2021), indicating membrane disruption and problems with intracellular signaling in AD brains. Mahajan et al. (2020) found disruptions in polyamine and transmethylation pathways, analogous to our finding of methionine and S-adenosylmethionine level changes.

Our findings further support the notion that disturbed metabolic processes in the brains of individuals with AD play a role in the pathogenesis of the disease. Similarities between our results and those of previous studies support both the accuracy of our findings and the need to explore metabolically based models for early detection and intervention of Alzheimer’s Disease.

5. Conclusion

We examined the metabolic disturbances occurring in the brains of individuals with AD, focusing on significant abnormalities in glucose metabolism, lipid processing, amino acid turnover and oxidative stress mechanisms. We observed considerable declines in glucose

utilization, especially in the hippocampus and frontal cortex, together with increased oxidative stress and disruptions in neurotransmitter metabolic pathways. Emerging evidence suggests that such metabolic disorders lie at the heart of AD development and share overlap with characteristic pathological changes. Yan et al., 2020).

Our results reveal that metabolic abnormalities contribute to the development as well as the clinical manifestations of Alzheimer's Disease. Our results are in agreement with major metabolomic studies (Ardanaz et al., 2022), confirming their significance on the field. Recent findings by Mahajan et al. further support the idea that molecular shifts occur at an early stage and may enable reliable detection of AD in the preclinical period. Moreover, highlighting that lipid and amino acid pathways are affected reveals potential new treatment strategies that could help restore energy balance and reduce neuroinflammation.

An examination of the biochemical changes associated with Alzheimer's Disease may provide new strategies for early detection and novel approaches for treating the condition. Further investigations should aim to establish the pattern of these metabolic changes as well as to evaluate whether identified biomarkers are suitable for clinical applications. These findings highlight the unique contribution of brain metabolism in understanding AD and emphasize the need to incorporate metabolic data into innovative diagnostic and treatment approaches.

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