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Abstract

Alzheimer's disease (AD) is a neurological disorder, a condition that significantly impacts both physical and mental health and ultimately leads to death.

Chemical, Environmental, and Molecular Perspectives; Diagnostic Biomarkers; and Iraqi Studies Insight into Alzheimer's Disease: A Review Article

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Alzheimer's disease is the seventh major cause of death, disability, and dependence. Several Determinants for dementia include depression, social isolation, inactivity, alcohol consumption, smoking, obesity, diabetes, high blood pressure, and age. Additionally, smoking, depression, and social isolation are notable risk factors.

The article provides a recent survey of prevalent data for staging and diagnosis of AD, regarding the role of epigenetic, chemical, and environmental factors, Classification of different indicators for early identification and prognosis in AD, and Diagnostic approach of AD, and studies the relationships among Alzheimer's disease, diabetes mellitus, and hypertension. Additionally, Research highlights the profound impact of previous studies conducted in Iraq.

Oxidative stress and metal ions are examples of chemical and environmental factors. Modifiable environmental variables, such as nutrition, exercise, and cognitive engagement, significantly influence AD. Advances in biomarker analysis (e.g., β -amyloid A β , Tau, apolipoprotein E4 APOE ϵ 4) and neuroimaging techniques, including MRI and PET scans, have revolutionized diagnostic approaches, enabling earlier detection and intervention. The vital interaction between hereditary and environmental factors alters the epigenetic landscape in AD, affecting gene expression patterns linked to major clinical processes underlying disease etiology.

The study concludes that Diabetes, hypertension, elderly individuals, low income or socioeconomic status, limited education, hearing or vision impairments, and functional limitations are associated with increased risk of falls. In addition to epigenetic factors, chemical and environmental factors also serve as risk factors for Alzheimer's disease (AD).

Keywords: Alzheimer's disease, Epigenetic factor, β -amyloid (A β), Chemical and Environmental Factors.



Introduction

The disease known as Alzheimer's is an incurable neurological disorder that mainly reduces mental function in older adults. AD is a global disease that mainly affects those over 65 (1). As reported by public health projections, 132 million individuals globally will have dementia by 2050 (2,3). AD is a public type of dementia, posing growing global challenges (4). Environmental, genetic, and age factors contribute to the complicated etiology of (AD). In addition, the current study focuses on cholinergic systems, amyloid and tau proteins, oxidative stress, metal ions, glutamate excitotoxicity, the microbiota-gut-brain axis, and aberrant autophagy (4). The Formation of amyloid beta plaques and tau protein tangles in the brain, together with neuroinflammation and synaptic dysfunction, is a characteristic of AD. The APOE ϵ 4 allele and mutations in the PSEN1, PSEN2, and APP genes are examples of genetic variables that enhance (5). AD is a neurological disease that causes cognitive impairment. The creation of "plaques" of excess fibrous tissue in the brain is one of the symptoms. Histopathological studies have shown that extracellular molecules, such as ApoE, serum amyloid P, and GAGs (primarily HSPG), are frequently accumulated in the brains of AD patients (6). Aggregated amyloid-beta ($A\beta$), both soluble and insoluble, can either initiate or intensify the AD mechanism. Researchers are studying lecanemab, an antibody that binds strongly to certain forms of amyloid-beta, in people with early AD (7). Metal ions have an important effect on the Accumulation of the amyloid- β peptide ($A\beta$), which is associated with AD. Higher concentrations of metal ions in AD patients' amyloid plaques lend credence to the theory that the deterioration of metal homeostasis is connected to the

emergence of AD disease (8). Immunocompetent cells, including microglia, govern the brain's intrinsic immune system. Moreover, the brain is susceptible to innate defensive mechanisms that involve inflammation (9). Amyloid Beta accumulation, tau protein pathology, neuroinflammation, neurodegeneration, and cerebrovascular dysfunction are the defining characteristics of AD, a severe neurological disorder (10). These elements stimulate immune system cells to enter the brain, which can exacerbate clinical symptoms and reduce the number of neurons in AD patients (11). Recent research reveals that peripheral immune cells, such as neutrophils, lymphocytes (T, B), NK cells, and monocytes, may invade cerebral arteries and parenchyma in AD, even though the central nervous system's (CNS) local immune cells, known as microglia, are crucial in AD.

These cells are involved in regulating inflammation and immunity, which is anticipated to be crucial for future immunotherapy. Considering how important peripheral immune cells are in AD (10). Multiple factors, mostly age-related causes of sporadic AD, include risk factors such as diabetes and cardiovascular or cerebrovascular disorders (12).

Etiology, causative, and risk factor

Epigenetic factor

Epigenetic regulation is a dynamic, reversible process that influences transcriptomic outcomes. Histone alterations, DNA methylation, and noncoding RNAs control the 3D chromatin structure and transcription factor activation. The enzymes responsible for these changes react to certain intracellular metabolic and paracrine



stimuli. Even though it is widely accepted that aging is associated with altered epigenomic dynamics and dysfunctional metabolic processes that may contribute to neurodegeneration, disease-related genetic variations can alter epigenomic characteristics (13). Although AD is thought to be triggered by hereditary factors, its exact etiology is yet unknown. Even though genetic variants, such as mutations in the APP, PSEN1, and PSEN2 genes, are identified and inherited according to Mendelian inheritance patterns (14). Age is a critical risk factor for AD, with histone alterations, mitochondrial DNA methylation, DNA methylation and hydroxymethylation, and non-coding RNAs (ncRNAs) being implicated, which are typical of epigenetic pathways that control gene expression, which is closely linked to neuron plasticity and integrity, thereby influencing learning and memory development, despite the exact mechanisms remaining unclear (15).

Chemical and Environmental Factors

Amyloid-beta and phosphorylated Tau aggregation in the brain are markers of AD (16). A β and p-tau biomarkers identified via imaging and cerebrospinal fluid analysis may indicate a higher risk of AD, aiding in accurate diagnosis and prognosis, particularly in relation to other chronic diseases (17). Globally determined non-genetic variables include exposure to volatile anesthetics, risky metals, industrial chemicals, electromagnetic fields, air pollution, and pesticides at work. Furthermore, the etiopathogenesis of AD may be influenced by certain pre-existing medical disorders such as cancer, depression, traumatic brain injury, diabetes, dyslipidemia, hypertension, and stroke. Other significant indicators include body mass index, cognitive function, physical exercise, and

lifestyle choices such as alcohol and caffeine use (14).

Alzheimer's disease and Metal ions

Recent studies revealed that various metals contribute to the pathogenesis of AD by disrupting cellular homeostasis, with aluminum being the most extensively researched. Long-term aluminum exposure, particularly among miners, correlates with higher AD-related mortality rates. Other metals such as mercury, zinc, copper, cadmium, magnesium, and manganese are also identified as risks. In contrast, lead, arsenic, and cadmium exacerbate A β peptide formation and "senile" plaques in key brain regions via triggering the "amyloidogenic cascade".

Alzheimer's disease and oxidative stress

Oxidative damage plays a crucial part in the etiology of Alzheimer's disease. The brain's function and structure are severely influenced by steroid hormones and mediators, such as testosterone, estrogen, and glucocorticoids (18).

Alzheimer's disease and acetylcholine

Milan Nemy's research shows that alterations in cholinergic white matter pathways occur in individuals with subjective cognitive decline before the evident changes associated with mild cognitive impairment and AD. This study indicates that the integrity of cholinergic pathways is a more reliable indicator of early AD stages compared to traditional volumetric measurements (19).

Sorting of several indicators for AD Estimation and early diagnosis

Through structural alterations that alter the accessibility of certain DNA sequences for transcriptional machinery, epigenetic processes reg-



ulate gene expression. Chromatin, which is composed of long DNA segments wrapped around histone proteins such as H2A, H2B, H3, and H4, tightly packs DNA into the chromosome (20). This extensive analysis encompasses numerous areas, including histone modification indicators, mitochondrial markers, long non-coding RNA markers, microRNA biomarkers, and DNA methylation biomarkers.

DNA methylation markers

One epigenetic process that controls gene expression is DNA methylation. A group of enzymes called DNA methyltransferases (DNMTs) methylate DNA (21). After a one-carbon metabolic cycle started by enzymes, S-adenosylhomocysteine is transformed into S-adenosylmethionine through methylation of DNA. Homocysteine, an intermediate in this cycle, is linked with a higher risk of cerebrovascular disease and AD (22). Understanding the significance of DNA methylation in the pathophysiology of AD requires examining the methylation status of specific genes (23).

(miRNA) microRNA markers

miRNAs have a major role in AD and exhibit biphasic expression, specifically affecting autophagic activity. In early-stage AD, miR-331-3p and miR-9-5p are greatly reduced (24). In the late stage of AD, high-bred autophagy is linked with elevated miRNAs, suggesting decreased autophagic activity. These miRNAs affect A β accumulation and may be used as indicators to differentiate between the early and late stages of AD by targeting the autophagy receptors Sqstm1 and Optn. Assessments of autophagic activity and their levels may serve as diagnostic differentiators (25).

Modification of Histone in AD

The ϵ 4 allele of APOE is the primary genetic risk factor for late-onset AD (LOAD), and its effect is compounded by various non-genetic factors, including environmental and lifestyle influences, which collectively increase the risk of developing the condition (26,27). Chromatin shape and transcription factor accessibility are two mechanisms by which histone acetylation and deacetylation affect gene transcription (28).

Diagnostic approach to Alzheimer's disease psychology diagnosis

Detecting, evaluating, and differentiating, diagnosing, and treating AD are all steps in the diagnostic process. Clinicians should use appropriate tests, including FDG-PET, after initial assessments. Key tools include the A-IADL-Q, A β , Ach, BG, cerebrospinal fluid evaluation, and Functional Activities Questionnaire (FAQ). A primary care physician may refer the patient for further clinical assessment based on symptoms (3).

Brain imaging, MRI, and PET

Alzheimer's and dementia are linked to the gradual death of brain cells. Although brain imaging is utilized to diagnose dementia, it is insufficient to diagnose AD since age-related and Alzheimer's-related brain changes are comparable. However, brain imaging can help with basic dementia diagnosis, brain tumors, strokes, severe bleeding, and other brain diseases (30).

Laboratory Diagnosis of Alzheimer's diseases Cerebrospinal fluid biomarkers

β -amyloid (A β) buildup, excessive tau phosphorylation, synaptic dysfunction, and neuroinflammation are among its main pathologies. Biomarkers such as cerebrospinal fluid A β 42, T-



tau, P-tau, synaptic proteins, neuroinflammatory agents, and dysregulated microRNAs provide crucial targets for early detection (31). Cerebrospinal fluid biomarker assays might be employed to identify Peptides such as tau and A β , and, in most individuals, modifications in these biomarkers can be recognized sooner than changes in neuroimaging biomarkers (32).

Blood biomarker

Blood-based biomarkers, like plasma assays for phosphorylated tau (p-tau), enhance the diagnosis and prognosis of AD. With the rise of anti-amyloid- β immunotherapies, differentiating AD from other neurodegenerative diseases has become increasingly accurate (33).

Material and Methods:

Search Procedures:

A systematic review strategy was utilized in accordance with PRISMA 2020 guidelines. Comprehensive searches were conducted across the journals PubMed, Scopus, Web of Science, EMBASE, and the Cochrane Library to locate relevant papers. Additional studies reviewed the reference lists of highlighted articles and grey literature sources (dissertations and conference papers). The search included articles published up until March 2025, regardless of locale, and was limited to English-language studies.

Boolean operators have been used in search strings to combine disease-associated words with biomarker categories. These include:

- (AD or cognitive decline or dementia).
- (Chemical and Environmental Factors β -amyloid (A β) OR AD and oxidative stress OR AD and acetylcholine OR AD and Metal ions).
- (Epigenetic factor or DNA methylation markers OR (miRNA) microRNA markers OR Modification of Histone in AD).

- (Laboratory Diagnosis of Alzheimer's OR Cerebrospinal fluid biomarkers OR Blood Biomarker Salivary biomarkers).
- (AD and Diabetes mellitus, AD and hypertension).

To enhance the sensitivity and specificity of databases, these sets were concatenated.

Evaluation of Study Selection and Quality

Two impartial reviewers reviewed all titles and abstracts obtained from database searches to exclude irrelevant research papers. After that, full-text publications were evaluated according to the established inclusion and exclusion criteria, with emphasis on research identifying molecular, environmental, chemical, biochemical, or diagnostic biomarkers associated with AD. The PRISMA 2020 criteria for analytical reviews were used to assess the methodological quality of the included studies, with special emphasis on the robustness of stated detection limits, Consistency of biomarker tests, and clarity of the research design.

Consequences of Bias

Several methods were used to address potential causes of bias. To reduce publication bias, only peer-reviewed publications were included. To reduce selection bias, the inclusion and exclusion criteria were closely applied. To reduce reviewer bias, two reviewers conducted independent duplicate screening and quality evaluation; any differences were resolved by consulting a third reviewer. These protocols evaluated research on biochemical, chemical, environmental, molecular, and diagnostic biomarkers in Alzheimer's disease, ensuring consistency, transparency, and reliability.



Inclusion Criteria and Exclusion Criteria

Inclusion Criteria

1. Population: Individuals with AD, moderate cognitive impairment (MCI), or genetic risk.
2. Objectives: Studies on genetic and biochemical indicators, such as the APOE ε4 allele and polygenic risk scores, as well as oxidative stress markers, tau proteins, and amyloid β.
3. The study design includes randomized controlled trials, cohort studies, case-control analyses, and systematic reviews and meta-analyses
4. Results: Comprehensive studies of genetic or biochemical correlations with AD risk, diagnosis, or progression.
5. Publication Category: Peer-reviewed journal articles written in English.

Exclusion Criteria

1. Research on neurological conditions unrelated to AD is an insignificant topic.
2. Poor quality: Lack of control groups, limited sample sizes without statistical rigor, or high bias risk.
3. Conference abstracts, editorials, dissertations, and grey literature are not subject to peer review unless specified differently.
4. Animal-only research: Unless it directly relates to human biochemical, hematological, or genetic processes.
5. Language limitations: Publications authored in languages other than English are often excluded, which leads to discrimination.

Table 1: Inclusion and Exclusion Criteria

Types	Inclusion Criteria	Exclusion Criteria	References Set priorities
A sample	AD, MCI, and genetic risk groups	Dementias other than AD	Scopus and PubMed
Emphasis	Genetic and biochemical markers	Unrelated to neurological conditions	The Web of Science
The Design	Cohort, case control, RCTs, and systematic reviews	Biased and poorly planned research	The Cochrane Library
Results	Genetic and biomarker correlations with AD	Uncertain or absent results	Journals of Neurology
Type of publication	English, peer-reviewed	Editorials, abstracts, and non-peer-reviewed	High-impact publications



Results

Table 2: Hematological and Biochemical Characteristics of AD in Iraqi Patients

Name of Parameter	Significant Features	Results in Iraqi Patients (Previous Studies)
Lipid Disorders, such as higher (Cholesterol, Triglycerides)	Dyslipidemia (high LDL, low HDL, and elevated TG) increases the risk of vascular disease and the production of amyloid plaque, which accelerates AD.	(Serum Lipid Profile in Iraqi Patients with Alzheimer's Disease) : found that AD patients had significantly higher TG and cholesterol levels than healthy controls (34).
Protein Alterations – Albumin	Low serum albumin levels reflect oxidative stress and poor cognitive outcomes; albumin also acts as an antioxidant and a transport protein.	(Biochemical Alterations in Serum Albumin Levels in Alzheimer's Disease Patients in Iraq): Found lowered albumin concentrations in AD patients, indicating impaired antioxidant defense (35).
Protein Alterations – Hemoglobin	Altered hemoglobin levels are linked to hypoxia, oxidative stress, and neurodegeneration.	(Evaluation of Hematological Parameters in Iraqi Alzheimer's Patients) –: Observed altered hemoglobin levels in AD patients, supporting the role of oxygen transport and oxidative stress in disease pathology (36).
Iron Toxicity	Excess iron promotes free radical formation via Fenton reactions, leading to neuronal injury and amyloid aggregation.	(Assessment of Iron Overload and Oxidative Stress in Alzheimer's Disease Patients in Iraq) – Found higher serum iron levels and markers of toxicity in AD patients, suggesting iron dysregulation contributes to disease progression (37).

This Iraqi research together demonstrates that AD is not just a brain issue but also encompasses systemic metabolic, biochemical, and hematological disorders. The development of the condition is influenced by iron-driven oxidative stress, dyslipidemia, hypoalbuminemia,

anemia, and inflammation. This highlights the significance of multi-parameter biomarker panels (lipids, albumin, hematological, iron/oxidative stress) for early identification of AD patients (38-40).



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Table 3: Inflammatory and Anti-Inflammatory Marker Alterations in AD

Name of Parameter	Significant Features	Results in Iraqi Patients (Previous Studies)
Pro-inflammatory cytokines	Elevated levels of IL-1 β , IL-6, and C-reactive protein (CRP) contribute to neuroinflammation and neuronal damage.	(Serum Cytokine Levels in Iraqi Patients with Alzheimer's Disease) : Reported significantly higher IL-1 β and IL-6 levels in AD patients compared to controls (41).
CRP (C-reactive protein)	Marker of systemic inflammation; elevated CRP linked to cognitive decline and vascular contributions to dementia.	(Evaluation of C-Reactive Protein in Iraqi Alzheimer's Patients) – Found elevated CRP levels in AD patients, suggesting systemic inflammation plays a role (42).
Reduced anti-inflammatory markers	Lower levels of protective cytokines (e.g., IL-10) and antioxidant defenses exacerbate neurodegeneration.	(Assessment of Anti-Inflammatory Cytokines in Alzheimer's Disease Patients in Iraq) – : Reported reduced IL-10 levels, indicating impaired anti-inflammatory response in AD patients (43).

According to all of this research, people with AD in Iraq had a markedly inflammatory profile with decreased levels of anti-inflammatory cytokines (IL-10, TGF- β) and elevated levels of pro-inflammatory cytokines (IL-1 β , IL-6, CRP). This cytokine imbalance is associated with neuronal damage and cognitive deterioration, especially when

AD appears. Regional biomarker studies highlight the roles of systemic and neuroinflammation, with elevated IL-1 β , IL-6, and CRP, and decreased cytokines that reduce inflammation, indicating potential biomarkers and therapeutic targets (44).

Table 4: APOE Polymorphism and Apelinergic Peptide Changes as Biomarkers of AD in Iraq

Name of Parameter	Significant Features	Results in Iraqi Patients (Previous Studies)
ApoE polymorphism	The most significant genetic risk factor for late-onset AD is the ApoE ϵ 4 allele, which affects lipid metabolism and amyloid deposition.	(Association of Apolipoprotein E Polymorphism with Alzheimer's Disease in Iraqi Patients) The ApoE ϵ 4 allele was shown to be considerably more common in Iraqi AD patients than in controls (45).
Apelin-17	A peptide that has a role in vascular control, anti-inflammatory signaling, and neuroprotection	(Evaluation of Apelin-17 Levels in Iraqi Alzheimer's Patients) : Reported decreased Apelin-17 concentrations in AD patients compared to controls, indicating impaired neuroprotective signaling (46).



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An Iraqi study shows that AD is associated with both genetic and peptide biomarkers: lower levels of Apelin 17 indicate reduced neuroprotective signaling, while APOE polymorphisms, particularly the $\epsilon 4$ variant, increase the risk. They highlight how peptide imbalance and genetic predisposition interact in the pathology of AD. These Findings highlight the demand for integrated biomarker panels that include peptide (Apelin 17, Elabela) and genetic (APOE) markers for early identification and monitoring in Iraqi AD patients (47)(48).

Conclusion

The study concludes that biological, environmental, chemical, and epigenetic factors are risk factors for AD. Among various methods for diagnosing AD, Apolipoprotein E (APOE) is a genetic biomarker based on the accumulation of β -amyloid ($A\beta$) in the blood. Together, these Iraqi investigations reveal that AD is a brain condition with systemic metabolic, biochemical, and hematological alterations. Dyslipidemia, hypoalbuminemia, anemia, inflammation, and the oxidative stress caused by iron all aid in the development of illness.

Authors contributions

All authors contributed to the collection of data, the preparation of the draft, and the review and approval of the final version of the manuscript.

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