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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 inclusive 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 research provides a recent review of prevalent data on the staging and diagnosis of AD, including the role of epigenetic, chemical, and environmental factors; classification of different indicators for early identification and prognosis in AD; and the Diagnostic approach to AD. Additionally, Research highlights the profound impact of previous studies conducted in Iraq. chemical and environmental factors. Environmental factors that can be altered, such as diet, exercise, and mental activity have a big impact on AD. Diagnostic methods have been transformed by advances in biomarker identification (e.g., β -amyloid $A\beta$, Tau, Apo lipoprotein E4 APOE $\epsilon 4$) and neuroimaging techniques (e.g., MRI and PET scans). enabling earlier detection and intervention.

The vital interaction between hereditary and environmental variables alters the epigenetic landscape in AD, affecting gene expression patterns linked with major clinical processes linked with disease etiology. These Iraqi studies collectively show that ad is not only a neurological disorder but also involves systemic metabolic, biochemical, and hematological changes. The study concludes that epigenetic factors, chemical and environmental factors serve as risk factors for Alzheimer's disease (AD).

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



Introduction

The disease known Alzheimer's is an incurable neurological disorders that mainly reduce mental in older adults. AD is a global disease that mainly alters those over 65 (1). As reported by Public health projections, 132 million individuals Globally will suffer from 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, cholinergic systems, amyloid and tau proteins, oxidative stress, metal ions, glutamate excitotoxicity, the microbiota-gut-brain axis, and aberrant autophagy are the main topics of current study (5). The Formation of amyloid beta plaques and tau protein tangles in the brain, together with neuroinflammation and synaptic dysfunction, are characteristics of AD. The APOE ϵ 4 allele and mutations in the PSEN1, PSEN2, and APP genes are examples of genetic variables that enhance (6). AD is a neurological disease that causes cognitive impairment. The creation of "plaques" excess fibrous tissue in the brain is one of the symptoms. Studies on histopathology have revealed that

extracellular molecules like as Apo lipoprotein E, serum amyloid P, and GAGs (mostly HSPG) are frequently accumulated in the brain tissue of AD patients (7). Aggregated amyloid-beta ($A\beta$), both soluble and insoluble, can either start or intensify mechanism of AD Researchers are studying lecanemab, a type of antibody that strongly attaches to certain forms of amyloid-beta, in people who have early AD (7).Metal ions has important effect on the Accumulation of amyloid- β peptide ($A\beta$), which is connected to 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, involving 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 exacebrate clinical symptoms and cause AD patients' neurons to dimmish (11). Recent research reveal that peripheral immune cells, such as neutrophils, lymphocytes (T, B), NK cells, and monocytes, may invade cerebral arteries and parenchyma in AD, despite the fact that the central nervous system's (CNS) local immune cells, known as microglia, are crucial in AD.

These cells are involved in the control of inflammation and immunity, which is anticipated to be crucial for immunotherapy in the future. 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 and reversible process that impacts 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,

which might affect neurodegeneration, disease-related genetic variations changing epigenomic characteristics (13). Although AD is thought to be triggered by hereditary factors, its exact etiology is yet unknown. Even though genetic variables such as mutations in the APP, PSEN1, and PSE2 genes are identified and inherited according to the Mendelian pattern (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 anesthesia, 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 a person's body

mass index, cognitive function, physical exercise, and lifestyle choices like alcohol and caffeine usage (13).

Alzheimer's disease and Metal ions

Recent studies revealed various metals enhance 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, while 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 the steroid hormones as well as mediators such as testosterone, estrogen and glucocorticoids hormones (18).

Alzheimer's disease and acetylcholine

Milan Nemy's research shows that alterations in cholinergic white matter pathways appears in individuals with subjective cognitive loss prior to the evident changes linked to 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



regulate gene expression. Chromatin, which is made up of lengthy DNA segments encased in histone proteins, such as a pair of the H2A, H2B, H3, and H4 core histones, firmly packs DNA into the chromosome (20). This extensive analysis encompasses numerous a reassuch as 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 DNA methylation's significance in the pathophysiology of AD requires examining the methylation state of certain 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 late-stage of AD, highered autophagy is linked with elevated miRNAs, suggesting decreased autophagic activity. These miRNAs affect A β accumulation and may be utilized as indicators to differentiate between early and final 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 ways that 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 ought to employ the right tests including FDG-PET after initial assessments. Key tools include the A-IADL-Q, A β , Ach, BG, cerebrospinal fluid evaluation, 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 and tau excessive phosphorylation, synaptic dysfunction, and neuroinflammation are among its main pathologies. Biomarker like 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 biomarkers 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 following data in the journals PubMed, Scopus, Web of Science, EMBASE, and the Cochrane Library to locate relevant papers. Additional studies covered the reference lists of highlighted articles and grey literature sources (dissertations, conference paper). The search included articles published up until March 2025, despite 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:

(Alzheimer's disease or cognitive decline or dementia)

- (Chemical and Environmental Factors β -amyloid (A β) OR Alzheimer's disease and oxidative stress OR Alzheimer's disease and acetylcholine OR Alzheimer's disease 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)
- (Alzheimer's diseases and Diabetes mellitus Alzheimer's disease and hypertension)

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

Evaluation of Study Selection and Quality

All titles and abstracts obtained from the database searches were reviewed by two impartial reviewers to exclude research papers that weren't relevant. After that full-text publications were evaluated in accordance with the set inclusion and exclusion criteria with an emphasis on research that revealed molecular, environmental, chemical, biochemical or diagnostic biomarkers connected to AD. The PRISMA 2020 criteria for analytical reviews was used to assess the methodological quality of the included studies paying special emphasis to the robustness of stated detection limits, Consistency of biomarker tests and clarity of research design.

Consequences of Bias

A number of methods were used to address potential causes of bias. To lower the possibility of publishing 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 carried out independent duplicate screening and quality evaluation; differences were settled by consulting a third reviewer. These protocols evaluated research on biochemical, chemical, environmental, molecular, and diagnostic



biomarkers in Alzheimer's disease, consistent, transparent, and reliable.

5. Publication Category: Peer-reviewed journal articles written in English.

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.

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 or 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 demonstrate 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 AD patients' early identification (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 these research, people with AD in Iraq had a markedly inflammatory profile with decrease 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 with cognitive deterioration, especially

when AD is appeared. Regional biomarker studies highlight the role 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 Purinergic Peptide Changes as Biomarkers of AD in Iraq

Name of Parameter	Significant Features	Results in Iraqi Patients (Previous Studies)
Ape polymorphism	The most significant genetic risk factor for late-onset AD is the Ape ϵ 4 allele, which affects lipid metabolism and amyloid deposition.	(Association of Apolipoprotein E Polymorphism with Alzheimer's Disease in Iraqi Patients) The Ape 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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Iraqi study shows that AD is associated with both genetic and peptide biomarkers: lower levels of Apelin 17 indicate a lack of neuro-protective signaling, while APOE polymorphisms particularly the $\epsilon 4$ variant higher 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, Ellabell) and genetic (APOE) markers for early identification and monitoring in Iraqi AD patients (47)(48).

Conclusion

The study results to the conclusion that biological and environmental, chemical, and epigenetic parameters are risk factors for AD. With various methods for diagnosing AD utilizing salivary biomarkers, cerebrospinal fluid biomarkers, and blood biomarkers 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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