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The impact of cytokines, hormones, and trace elements on Alzheimer's disease progression: A case-control study

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Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral disturbances. The aims of the study is evaluate the impact of cytokines, hormones, and trace elements on the progression of Alzheimer's disease. A case control study involved 150 Alzheimer's disease patients (75 males, 75 females) and 75 controls (37 males, 38 females) aged 64–75 years. Diagnosis was confirmed by neurologists, with ethical approval and informed consent obtained. Blood samples were collected, and serum was analyzed for IL-6, TNF-α, IL-10, amyloid beta protein, tau protein, homocysteine, cortisol, estradiol, testosterone, zinc, copper, and selenium using ELISA, Cobas, and spectrophotometry. This study found significant differences between Alzheimer's disease patients and controls. Alzheimer's disease patients showed increased levels of cytokines IL-6 and TNF-α, and decreased IL-10. Hormonal assessments revealed higher cortisol and lower estradiol and testosterone. Trace elements like zinc and selenium were lower, while copper was higher. Key biomarkers (amyloid beta, tau protein, homocysteine) were also elevated in AD patients. This study highlights the role of cytokines, hormones, and trace elements in Alzheimer's disease development. Increased levels of cytokines, cortisol, and trace elements suggest inflammation and metabolic imbalance in Alzheimer's disease. Monitoring these biomarkers could aid in disease management and therapeutic intervention.

Keywords: Alzheimer's disease; cytokines; hormones; trace elements; biomarkers; cognitive function.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that impairs memory, thinking, and language. It is the most common form of dementia in older adults, initially causing mild forgetfulness and eventually leading to complete care dependency. The early stages of AD are marked by the accumulation of amyloid β-protein (Aβ) in senile plaques, neurofibrillary tangles (NFTs) formed by tau protein, and neuronal loss, all contributing to cognitive decline (Biglari et al., 2020; Chan et al., 2021). A definitive diagnosis of AD currently requires postmortem brain autopsy (Scheltens et al., 2021).

Genetic factors account for 60–80% of AD risk, with over 40 inherited risk factors identified. The ε4 allele of apolipoprotein E (APOE) is particularly associated with late-onset AD, present in about 16% of individuals. Early-onset familial AD is often linked to mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes (Eratne et al., 2018). Chronic inflammation is a key driver of AD progression, impairing neuronal function. Cytokines play a central role in neuroinflammation. Aβ activates astrocytes and microglia, triggering the release of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-2, IL-12, and IFN-γ, which exacerbate AD pathology (Liu et al., 2023).

Conversely, anti-inflammatory cytokines such as IL-1ra, IL-33, and IL-10 are elevated in cerebrospinal fluid and plasma in AD, reflecting the body's attempt to counteract inflammation. Although extensive research targets cytokine modulation to slow AD progression, the precise roles of cytokines in AD pathogenesis remain unclear (Ahoon et al., 2024). A deeper understanding of cytokine-mediated neuroimmune interactions may facilitate the development of novel therapeutic strategies (Brosseron et al., 2014). Cytokines are signaling proteins crucial for initiating, sustaining, and regulating immune responses, as well as mediating cell-to-cell communication. Alterations in cytokine levels, particularly in the Th1/Th2 balance, are linked to AD pathogenesis and disease severity (Hamad et al., 2024). Pro- and anti-inflammatory cytokines contribute to AD progression (Lateef et al., 2024).

Elevated IL-6 levels have been observed in the brains and plasma of AD patients and are implicated in disease-related neurodegeneration and behavioral abnormalities. MRI findings often show T2 hyperintensities consistent with demyelination in affected individuals (Lyra et al., 2021; Xu et al., 2021). TNF-α enhances AMPA receptor trafficking, increases glutamatergic signaling, and impairs long-term potentiation, further contributing to synaptic dysfunction in AD (Ren et al., 2021). Additionally, copper (Cu) dysregulation is implicated in AD. Elevated total and free serum Cu levels have been observed in AD patients (Eskici & Axelsen, 2012). Studies reveal higher copper concentrations in amyloid plaques of AD patients, where Cu directly binds to Aβ, promoting its aggregation and neurotoxicity. In vitro, Cu removal from Aβ reduces plaque formation and neuronal death (Squitti et al., 2014).

Zinc (Zn^{+2}) homeostasis also influences AD. Zn^{+2}-binding transcription factors, including NF-κB and p53, regulate APP expression. Zn^{+2} can modulate Aβ aggregation; while low Zn^{+2} levels protect neurons, excessive Zn^{+2} promotes Aβ fibril formation (Cuesta et al., 2009; Wang et al., 2023). Selenium (Se) deficiency is common in AD. Seleno-L-methionine and vitamin E mitigate oxidative stress and β-amyloid toxicity. Sodium selenite inhibits γ-secretase, reducing amyloid production (Corcoran et al., 2010). Higher selenium levels are associated with a significantly lower risk of AD, independent of other risk factors, with studies showing a 1.4-fold reduction in AD risk linked to increased blood selenium (Strumylaite et al., 2022). This study aims to evaluate the contributions of cytokines, hormones, and trace elements to AD progression, exploring their relationships with disease development and identifying potential targets for therapeutic intervention.

Materials and methods

The study was approved by the ethics committee at the Neurological Diseases Center, Nasiriyah General Hospital, under committee code 456, on October 1, 2024. All participants were fully informed about the study and provided written consent to participate. They were also assured that their personal information would remain confidential.

A case control study included 150 patients diagnosed with Alzheimer's disease (AD), comprising 75 males and 75 females, along

with a control group of 75 healthy individuals (37 males and 38 females). The age of participants ranged between 64 and 75 years. The diagnosis of AD was confirmed by specialized neurologists based on established clinical criteria. The study was conducted at the Neurological Diseases Center at Nasiriyah General Hospital from October 1, 2024, to February 10, 2025. Inclusion criteria encompassed patients diagnosed with Alzheimer's disease who consented to participate, while exclusion criteria included individuals with severe comorbid conditions, recent infections, or those undergoing immunosuppressive therapy. Ethical approval was obtained from all participants, who signed informed consent forms before enrollment.

Table 1
Comparison of gender, age, and marital status distribution

Category	Alzheimer's patients (75 men, 75 women)	Control group (75)	P-value
Total number	150	75	–
Men, %	50	49	0.82
Women, %	50	51	0.82
Mean age, years	68.5 ± 4.5	68.0 ± 4.3	0.68
Married, %	65	70	0.42
Single, %	20	15	0.50
Divorced, %	15	15	1.00

Blood samples were collected from all participants via venipuncture into sterile tubes. Serum was separated by centrifugation at 3,000 rpm for 10 minutes and stored at –80 °C until analysis. Biomarkers, including IL-6, TNF-α, IL-10, amyloid beta protein, tau protein, and homocysteine, were measured using enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's instructions (Bio-Techne, USA). Cortisol, estradiol, and testosterone levels were assessed using the Cobas analyzer, according to the manufacturer's protocol (Roche, Germany). Additionally, levels of zinc, copper, and selenium were quantified using a spectrophotometer based on the guidelines provided by the manufacturer (BioLabo, France).

Statistical analysis is used to describe data and draw conclusions from both continuous and categorical variables. The study data are presented as percentages and frequencies. For normally distributed variables, we used the dependent and independent t-tests (two-tailed). For non-normally distributed variables, we applied the Mann-Whitney U test, Wilcoxon test, and Chi-square test. A significance level of $P < 0.05$ was considered statistically significant.

Results

The study included 150 Alzheimer's patients (75 men and 75 women) and 75 controls, with equal gender distribution in both groups ($P = 0.82$). The mean age of patients was 68.5 ± 4.5 years, and 68.0 ± 4.3 years for controls, with no significant differences ($P = 0.68$). Marital status showed 65% of Alzheimer's patients were married compared to 70% in controls ($P = 0.42$), while 20% of patients were single compared to 15% in controls ($P = 0.50$), and 15% were divorced in both groups ($P = 1.00$).

Cytokine levels were significantly higher in Alzheimer's disease (AD) patients than in controls. IL-6 was 8.5 ± 2.1 ng/mL in AD patients, compared to 3.2 ± 1.1 ng/mL in controls ($P < 0.001$). TNF-α levels were 12.3 ± 3.0 ng/mL in patients, compared to 5.4 ± 1.5 ng/mL in controls ($P < 0.001$). IL-10 was 4.0 ± 1.0 ng/mL in AD patients, compared to 2.1 ± 0.8 ng/mL in controls ($P < 0.01$). These results indicate a significant association between AD and elevated cytokine levels.

Table 2
Assessment of IL-6, TNF-α, and IL-10 levels

Cytokine	Alzheimer's patients, ng/mL	Control group, ng/mL	P-value
IL-6	8.5 ± 2.1	3.2 ± 1.1	< 0.001
TNF-α	12.3 ± 3.0	5.4 ± 1.5	< 0.001
IL-10	4.0 ± 1.0	2.1 ± 0.8	< 0.010

Hormone levels showed significant differences between AD patients and controls. Cortisol was elevated at 19.5 ± 4.2 pg/mL in AD patients, compared to 12.0 ± 3.1 pg/mL in controls ($P < 0.001$). Estradiol decreased to 80.2 ± 15.0 pg/mL in AD patients, compared to 100.3 ± 20.5 pg/mL in controls ($P < 0.01$). Testosterone also decreased to 250 ± 50 pg/mL in patients, compared to 350 ± 70 pg/mL in controls ($P < 0.001$). These findings suggest hormonal changes associated with AD.

Table 3
Comparison of cortisol, estradiol, and testosterone levels

Hormone	Alzheimer's patients, pg/mL	Control group, pg/mL	P-value
Cortisol	19.5 ± 4.2	12.0 ± 3.1	< 0.001
Estradiol	80.2 ± 15.0	100.3 ± 20.5	< 0.010
Testosterone	250 ± 50	350 ± 70	< 0.001

Trace element levels showed significant differences between Alzheimer's disease (AD) patients and controls. Zinc levels decreased to 60 ± 10 μg/mL in AD patients, compared to 90 ± 15 μg/mL in controls ($P < 0.001$). Copper levels slightly increased to 1.0 ± 0.2 μg/mL in patients, compared to 0.9 ± 0.2 μg/mL in controls ($P < 0.05$). Selenium levels decreased significantly to 0.9 ± 0.3 μg/mL in AD patients, compared to 1.5 ± 0.4 μg/mL in controls ($P < 0.001$). These findings suggest significant alterations in trace element levels in AD patients.

Table 4
Evaluation of zinc, copper, and selenium concentrations

Trace element	Alzheimer's patients, μg/mL	Control group, μg/mL	P-value
Zinc	60 ± 10	90 ± 15	< 0.001
Copper	1.0 ± 0.2	0.9 ± 0.2	< 0.050
Selenium	0.9 ± 0.3	1.5 ± 0.4	< 0.001

Biomarker levels were significantly higher in Alzheimer's disease (AD) patients than in the control group. Amyloid β-protein was 250 ± 50 ng/mL in AD patients versus 150 ± 30 ng/mL in controls ($P < 0.001$). Tau protein levels were 100 ± 20 ng/mL in AD patients compared to 50 ± 10 ng/mL in controls ($P < 0.001$). Homocysteine levels were 12 ± 3 μmol/L in AD patients, compared to 8 ± 2 μmol/L in controls ($P < 0.001$). These findings indicate a strong correlation between AD and elevated biomarker levels.

Table 5
Analysis of amyloid beta protein, tau protein, and homocysteine

Biomarker	Alzheimer's patients	Control group	P-value
Amyloid beta protein, ng/mL	250 ± 50	150 ± 30	< 0.001
Tau protein, ng/mL	100 ± 20	50 ± 10	< 0.001
Homocysteine, μmol/L	12 ± 3	8 ± 2	< 0.001

Statistical analysis showed a strong positive correlation between biomarker levels and Alzheimer's disease diagnosis. The correlation coefficient for amyloid beta protein was 0.75 ($P < 0.001$), for tau protein 0.70 ($P < 0.001$), and for homocysteine 0.65 ($P < 0.01$). These results demonstrate that these biomarkers are significantly associated with Alzheimer's disease and provide valuable insights for its diagnosis.

Table 6
Association of amyloid beta protein, tau protein, and homocysteine

Biomarker	Correlation coefficient (r)	P-value
Amyloid beta protein	0.75	< 0.001
Tau protein	0.70	< 0.001
Homocysteine	0.65	< 0.010

Discussion

Alzheimer's disease (AD) is a severe neurodegenerative disorder marked by progressive cognitive decline. A key feature of AD is altered cytokine expression, particularly in pro-inflammatory and anti-inflammatory mediators such as IL-6, IL-10, and TNF-α (Choi et al., 2021). The interplay of these cytokines underscores the dual role of neuroinflammation in the pathogenesis of AD. Studies have shown significantly elevated cytokine levels in AD patients compared to healthy individuals and those with other neurological disorders, sugges-

ting their active involvement in disease progression (Pan et al., 2022). IL-6 is a multifunctional cytokine with both pro- and anti-inflammatory properties, particularly in AD. Hirano et al. (2021) reported significantly elevated IL-6 levels in the cerebrospinal fluid (CSF) and plasma of AD patients compared to age-matched controls. Baker et al. (2018) confirmed this, highlighting IL-6 as both a biomarker of inflammation and a regulator of blood-brain barrier stability and neuronal function in AD pathogenesis. Di Bona et al. (2009) observed higher IL-6 levels in AD compared to Parkinson's disease and vascular dementia, indicating a stronger inflammatory response in AD. Although IL-6 may initially counteract amyloid-β (Aβ)-induced damage, its prolonged elevation exacerbates neurotoxicity through activation of inflammatory pathways, ultimately compromising neuronal integrity (Italiani et al., 2018). This dual role makes IL-6 both a potential therapeutic target and a marker of disease progression.

Similarly, IL-10 levels are elevated in AD despite its known anti-inflammatory role. This likely represents a compensatory response to chronic neuroinflammation. A meta-analysis by Torres-Acosta et al. (2020) reported significantly higher IL-10 concentrations in the plasma of AD patients. Ekert et al. (2018) explained that while IL-10 initially resolves inflammation, its chronic elevation in AD may suppress effective immune responses, inadvertently contributing to Aβ and tau pathologies. Interestingly, IL-10 levels in AD surpass those in overtly inflammatory diseases like multiple sclerosis, reflecting complex immune dysregulation in AD.

TNF-α, a key pro-inflammatory cytokine, is also elevated in both peripheral blood and CSF of AD patients. The higher TNF-α levels in AD compared to mild cognitive impairment suggest a role in disease progression. The TNF-α levels to be distinctly higher in AD than in frontotemporal dementia, likely due to differences in microglial activation (Ou et al., 2021). Chronic TNF-α elevation in AD exacerbates neurodegeneration by inducing synaptic dysfunction and neuronal apoptosis.

The higher prevalence of AD in women suggests a role for sex hormones in its development. Studies in cell and animal models indicate that testosterone (T) is closely linked to neuronal function and reduces Aβ accumulation in the brain. By activating the androgen receptor (AR) signaling pathway, T-enhances microglial phagocytosis, promotes Aβ clearance, and suppresses inflammation (Yeung et al., 2023). In women, estrogens protect neurons from damage, and their decline during menopause is thought to be a key factor in AD development. Plasma androgens and sex hormone-binding globulin (SHBG) levels drop gradually with age in postmenopausal women (Lopez-Lee et al., 2024). Since estradiol is primarily derived from testosterone through aromatase activity in extra-gonadal tissues, the age-related decline in plasma androgens significantly reduces estradiol levels. This hormonal shift may exacerbate neuronal vulnerability and contribute to AD risk (Lam et al., 2021).

Trace elements such as zinc (Zn), selenium (Se), and copper (Cu) are essential for brain health, influencing oxidative stress, enzymatic activity, and neuronal signaling. In AD, imbalances in these metals are common, with notable deficiencies in zinc and selenium, as well as altered copper levels, compared to healthy individuals and patients with other neurodegenerative diseases (Ala et al., 2007). These studies suggest that trace element imbalances play a significant role in AD development, warranting further investigation of their therapeutic potential (Conrad & Proneth, 2020).

Zinc is critical for synaptic plasticity and memory formation, but its levels are significantly reduced in AD. Rembach et al. (2014) found lower serum zinc levels in AD patients compared to healthy controls (Fasae et al., 2021). The zinc depletion promotes Aβ aggregateon, leading to plaque formation and oxidative stress. This decrease in zinc is more pronounced in AD than in Parkinson's disease or vascular dementia, possibly due to unique interactions between zinc and Aβ (Ho et al., 2022). Future research should explore how zinc dysregulation contributes to AD progression and how restoring zinc balance could mitigate cognitive decline.

Selenium, a vital component of selenoproteins, is also reduced in AD. Lei et al. (2021) found significantly lower serum selenium levels in AD patients compared to healthy controls and those with mild cognitive impairment (MCI), with selenium levels directly correlating with cognitive performance. Selenium protects against oxidative stress, which is particularly important given the brain's vulnerability to oxidative damage. Selenium depletion in AD is greater than in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), which also feature mitochondrial dysfunction and oxidative stress (Nguyen et al., 2023). Selenium deficiency impairs glutathione peroxidase activity, exacerbating oxidative damage and accelerating neurodegeneration.

The role of copper in AD remains complex and requires further investigation. Patel & Aschner (2021) reported lower CSF copper in AD patients, although serum copper may be normal or elevated in its non-ceruloplasmin-bound form. Impaired copper transport disrupts the activity of key enzymes such as cytochrome c oxidase and superoxide dismutase. In contrast to diseases like Huntington's disease, copper dysregulation in AD is closely linked to Aβ aggregation and tau hyperphosphorylation (Sehar et al., 2022).

In this study, Table 5 shows that AD patients have significantly higher levels of amyloid beta, tau protein, and homocysteine ($P < 0.001$) compared to the control group. These findings are consistent with studies identifying Aβ accumulation and tau hyperphosphorylation as central hallmarks of AD pathology, where amyloid plaques and tau tangles impair neuronal function and drive cognitive decline (Skalny et al., 2024). Elevated homocysteine levels contribute to oxidative stress, vascular injury, and neuroinflammation, further accelerating AD progression. While some studies report no significant association between homocysteine and AD, these biomarkers remain valuable for diagnosis and monitoring disease progression, and they represent promising therapeutic targets for future research (Zhang & Song, 2021).

Conclusion

This study demonstrates that elevated pro-inflammatory cytokines, cortisol, copper, and amyloid markers, along with reduced IL-10, sex hormones, zinc, and selenium, are strongly associated with Alzheimer's disease progression, indicating inflammation and metabolic dysregulation as key contributors.

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