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Abstract.

Alzheimer's disease is a neurodegenerative disease leading to a progressive and irreversible loss of mental functions. It is characterized by 3 stages according to the evolution and the severity of the symptoms. The authors of the present study aimed to investigate the levels of serum lipocalin-2, fetuin-A, and TNF-α in patients with Alzheimer’s disease.

Patients and Methods: 56 patients with Alzheimer’s disease (the first group), and another 25 healthy volunteers (control group) were enrolled in this cross-sectional study. The serum levels of lipocalin-2, fetuin-A, and Tumor necrosis factor (TNF-α) were determined with the use of the ELISA method.

Results: There was a significant elevation in serum lipocalin-2, and TNF-α levels in the AD group (88.68±32.1) and(42.28±5.05) respectively, compared to the control group (63±28.5), and (35.19±5.07) respectively, [p< 0.001]. A significant increase in serum concentration of lipocalin, TNFα with a reduction of fetuin-A could be considered an important phenomenon used for follow-up or prognosis and diagnosis of Alzheimer's disease.

Key words. Lipocalin-2, TNFa, Fetuin-A, Alzheimer’s disease.

Introduction.

Alzheimer's disease, a debilitating neurodegenerative disorder, stands as one of the most prominent forms of dementia worldwide, with an estimated 44 million people affected by its unforgiving grasp. Regrettably, this chronic and progressive condition is currently untreatable, and its multifactorial nature only adds to the complexity of finding a cure. The ramifications of Alzheimer's disease are far-reaching, affecting not only the afflicted individual but also their loved ones who watch as their memories fade and their cognitive abilities decline. As the world's population continues to age, the impact of Alzheimer's disease is only set to increase, making it a critical area of research and medical attention [1,2].

Alzheimer's disease (AD) is the most common subtype of dementia in the elderly, but there are still no curative options [3]. Alzheimer's disease (AD), a progressive and irreversible neurodegenerative disorder, is extensively characterized by the accumulation of two major pathological hallmarks in the brain cortex and hippocampus: amyloid-β peptide and tau protein. These abnormal protein deposits cause a complex cascade of pathophysiological events, including altered production, aggregation, and clearance of amyloid-β peptide, and hyperphosphorylation of tau protein, which leads to the formation of neurofibrillary tangles. In addition, these pathological processes trigger a local inflammatory response that contributes to neuronal destruction and tissue atrophy. The intricate interplay of these events ultimately leads to the gradual deterioration of cognitive functions in AD patients, affecting their memory, thinking, and behaviour, and severely impacting their quality of life and that of their families [4,5].

In recent years, there has been a significant shift in the way white adipose tissue (WAT) is perceived. It is no longer viewed as a mere storage organ that responds solely to afferent signals from hormone systems and the central nervous system. Rather, it is now widely recognized that WAT is a complex organ that is capable of producing a plethora of bioactive substances, including cytokines and hormones, collectively known as adipokines. These adipokines include leptin, visfatin, resistin, sex steroids, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and acylation-stimulating protein. Their role is not limited to physiological functions but also extends to inflammatory processes, thereby highlighting their involvement in the pathophysiology of various diseases. This new understanding of WAT and its multifaceted functions has opened doors to a plethora of research opportunities and therapeutic interventions [6-8].

Lipocalin-2, the fascinating and versatile adipose tissue-derived cytokine, which is also known as 24p3 and neutrophil gelatinase-associated lipocalin (NGAL), is a 25-kDa glycoprotein of immense importance, belonging to the lipocalin subfamily of small, secreted proteins that bind hydrophobic molecules, including retinoids, fatty acids, and various steroids. This remarkable molecule is known for its unique structure that contains eight beta-strands that form a β-barrel in a closed cup, which plays an essential role in its multifaceted functions and biological activities. From regulating iron metabolism to serving as a biomarker for various diseases, Lipocalin-2 continues to captivate researchers and medical professionals alike with its intriguing properties and potential therapeutic applications [9-11]. LCN2, also known as Lipocalin-2, is a fascinating adipose tissue-derived cytokine that plays a significant role in the immune system. This protein's expression is induced by a multitude of pro- and anti-inflammatory cytokines and factors, such as lipopolysaccharide (LPS), tumour necrosis factor-α (TNF-α), IL-1β, IL-6, or IL-17, in a variety of cell types. LCN2 is involved in a variety of physiological and pathological processes, including inflammation, infection, immunity, and cancer. This protein's ability to modulate the immune response and regulate the inflammatory process has piqued the interest of researchers worldwide. Its multifaceted roles and complex interactions with other proteins make it an intriguing subject for further study in the field of immunology [12].

Fetuin-A, a remarkable protein with a multitude of functions, is also known as α-2 Heremans-Schmid glycoprotein (AHSG) - a member of the cystatin superfamily of protease inhibitors.
This phosphorylated glycoprotein, which is comprised of three O-linked and two N-linked oligosaccharide chains, is a crucial member of the fetuin group of serum-binding proteins. Originating from the liver, fetuin-A is a major human secretory protein that plays a significant role in various biological functions, both normal and pathological. Among its many functions, fetuin-A is responsible for regulating bone metabolism, controlling protease activity, inhibiting vascular calcification, and promoting insulin resistance. Additionally, this protein is involved in the proliferation signaling of breast tumour cells and the migration of keratinocytes [13,14]. Fetuin-A, an intriguing and multifunctional glycoprotein, is predominantly synthesized by the liver, but it also has a presence in other human organs including the kidneys and the tongue. The synthesis of this vital protein is known to be downregulated by proinflammatory cytokines such as TNF, which is why it is classified as a negative acute-phase protein. This protein plays a crucial role in various physiological processes such as the regulation of mineralization and bone development, insulin signalling, and inflammation. Despite being discovered decades ago, researchers are still exploring the potential of Fetuin-A in various medical fields, making it a subject of great interest and importance [15,16]. Our study focuses on estimating the concentration of the lipocalin-2, Fetuin-A, and Tumor necrosis factor (TNF), in patients with AD.

Materials and methods.

The present study was carried out at the Research Center in Tikrit University. This study was performed on 112 individuals, 56 patients diagnosed with AD (20 men, 36 women), with a mean age of 79.4±5.0 years in the Kirkuk General Hospital of the Department of internal medicine, in Kirkuk governorates and 60 control healthy individuals (25 men, 31 women), matched for sex and age 78.7±4.0 between February 2020 to December 2021. Upon arrival at the healthcare facility, every patient was greeted by a friendly and compassionate staff member who provided them with a special questionnaire form. This form was designed to gather vital information about the patient's medical history and current condition to help the medical team provide the best possible care. The questionnaire included various fields that needed to be filled out such as the patient's name, address, gender, age, and any blood or genetic diseases they may have. Additionally, the patient's occupation was also included to help the medical team understand the potential impact of the patient's work on their health. However, the control group had some exclusion criteria that needed to be met to participate in the study. These criteria included the absence of concurrent neurological issues, severe anaemia, severe malnutrition, mental deficiency, severe and unchecked arterial hypertension, concurrent psychiatric issues or a history of psychological illness, cancer, HIV-AIDS, stroke, and alcoholism. By ensuring that the control group met these criteria, the medical team could accurately assess the efficacy of the treatment being studied and provide valuable insights into the best practices for patient care.

With the utmost care and precision, the researchers collected five millilitres of venous blood samples from both the control group of healthy volunteers and the patients, ensuring that the process was as minimally invasive as possible. The samples were then delicately transferred into test tubes, where they were left to clot under carefully controlled conditions. After a thorough clotting process, the samples were then subjected to a centrifugation process at 5000 rounds per minute for ten minutes to achieve optimal separation. Finally, the sera were delicately extracted and stored with the utmost care until they were ready to be assayed for laboratory investigations, marking a significant milestone in the researchers' quest for a deeper understanding of the human body's inner workings.

Levels of lipocalin-2, fetuin-A and TNF-α were measured with enzyme-linked immunosorbent assay (ELISA) kits BioPorto Diagnostics, Denmark).

In the realm of data analysis, the statistical package of social science (SPSS) version 23.0 for Windows was utilized to perform a comprehensive analysis of the dataset. To better understand the numerical variables, the means were calculated and presented alongside T-Test results for comparison between categorical variables. The selected level of significance for P values was set at less than 0.05, ensuring that only the most significant results were reported. Through this rigorous analysis, valuable insights were gained, and a deeper understanding of the data was achieved.

Results.

Clinical and laboratory characteristics of all patients with AD and healthy control subjects and a comparison between all groups are given in Table 1. A total of 56 patients (20 males, 36 females), of mean age 79.4±5.0 years, and 56 age- and sex-matched healthy controls were enrolled in this study.

Serum lipocalin-2 and TNF-α levels were significantly higher in the AD group (88.68±32.1) and (42.28±5.05) respectively, than in the healthy control group (63±28.5), and (35.19±5.07) respectively [P<0.001]. Fetuin-A was significantly lower in the AD group (109.5±10.8) than in the control group (128.4±16.5), [p<0.001].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AD group (n=56)</th>
<th>Control group (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79.4±5.0</td>
<td>78.7±4.0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>20/36</td>
<td>25/31</td>
</tr>
</tbody>
</table>

Table 2. Biochemical parameters of study groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipocalin-2 (ng/mL)</td>
<td>88.68±32.1*</td>
<td>63±28.5</td>
</tr>
<tr>
<td>TN-α</td>
<td>42.28±5.05*</td>
<td>35.19±5.07</td>
</tr>
<tr>
<td>Fetuin-A (ng/ml)</td>
<td>109.5±10.8</td>
<td>128.4±16.5*</td>
</tr>
</tbody>
</table>

*P < 0.001

Discussion.

Lipocalin-2, a protein that has recently been discovered to be secreted by adipocytes, has been found to act as both an autocrine and paracrine adipokine. This fascinating protein has been shown to have an antagonistic effect on the activity of inflammatory molecules, which play a key role in the development of inflammation, and also in the secretion of other adipokines. This means that Lipocalin-2 has the potential to...
act as a powerful regulator of the inflammatory response in adipose tissue, which could have important implications for the treatment of obesity and related metabolic disorders. In short, Lipocalin-2 is a truly novel and fascinating protein that is poised to revolutionize our understanding of adipose tissue biology and metabolic disease [17].

The LCN2 protein, a multifunctional protein that plays a pivotal role in various physiological processes, is capable of passing through the blood-brain barrier and entering the central nervous system (CNS) either actively or passively. Even though NGAL mRNA and protein are typically expressed at low levels in the brain under normal physiological conditions, the LCN2 gene expression is regulated by glucocorticoids, which are critical regulators of cognitive function. Moreover, LCN2 acts as an acute phase mediator in the CNS and serves as a potential protective factor in response to systemic inflammation. This finding is particularly significant given that inflammation has been linked to numerous neurodegenerative disorders, and the identification of new protective factors in the CNS may pave the way for novel therapeutic interventions that help prevent or alleviate these debilitating conditions [18-20].

The intricate workings of the central nervous system (CNS) have long been a subject of fascination for researchers seeking to understand the underlying mechanisms of various neurological disorders. One such disorder, Alzheimer's disease (AD), is closely linked to the presence of LCN2, a protein that promotes neuronal death and reactive gliosis while triggering insulin resistance (IR) in the CNS. Notably, postmortem brain regions affected by AD pathology, particularly the hippocampus, show robust increases in NGAL protein levels, further implicating LCN2 in the disease's progression. It is believed that LCN2-mediated neuronal sensitivity to toxicity in AD may be due in part to impaired clearance of this molecule from the brain, a phenomenon that has also been suggested in relation to Aβ1-42. These findings shed light on the complex interplay between various proteins and molecules in the CNS and hold promise for the development of targeted therapies to combat the devastating effects of AD [23].

The intricate web of biological mechanisms underlying the progression of Alzheimer's disease (AD) has been extensively studied, with mounting evidence suggesting the involvement of altered LCN (lipocalin) receptors and elevated levels of LCN2 in the central nervous system (CNS). These molecular changes may contribute to the pathogenesis of AD, including neuronal cell death, glia activation, and insulin resistance (IR), which are all hallmarks of this debilitating neurodegenerative disorder. In light of this, our present study aimed to shed further light on the role of LCN2 in AD progression by examining its levels in the serum of patients with AD compared to healthy controls [24]. Interestingly, our findings revealed a significant increase in serum LCN2 levels in patients with AD as compared to the control group, providing further evidence to support the involvement of LCN2 in AD pathogenesis. This finding is consistent with previous studies, such as the one conducted by Jang et al, which reported higher levels of LCN2 in AD patients, thus bolstering the case for its potential use as a biomarker for AD diagnosis and prognosis. These results underscore the importance of continued research into the complex molecular mechanisms underlying AD, with a particular focus on the role of LCN2 and related pathways, to develop more effective therapies and diagnostics for this devastating disease [21]. Choi et al. [23] stated that LCN2 triggers inflammation, and subsequently reduces cognitive function. Mucha et al and Bi F et al reported that astrocytes in neurodegenerative conditions are the main producers of NGAL, while psychological stress might mostly trigger NGAL expression in neurons [18,20].

Tumour necrosis factor (TNF) is a fascinating and complex pleiotropic pro-inflammatory cytokine that is produced by a variety of cells including adipocytes, neutrophils, activated lymphocytes, macrophages, and null killer cells and serves as a crucial mediator in a vast array of inflammatory disorders and neurodegenerative diseases such as Parkinson's disease and AD, making it a major focus of research in the medical community. Despite its important role in the body's immune response, TNF can also have detrimental effects on the body when produced in excess, leading to chronic inflammation and tissue damage, which has inspired a multitude of studies aimed at regulating and controlling TNF levels to combat these negative outcomes [25,26]. As an important pro-inflammatory cytokine, TNF-α plays a pivotal role in regulating the immune system and contributing to the pathogenesis of various inflammatory disorders. One of its most significant roles is interfering with insulin signalling in a variety of non-insulin-producing cells, which results in insulin resistance and impaired glucose uptake, ultimately leading to the development of type 2 diabetes mellitus. Moreover, TNF-α is known to initiate the acute phase response, which is a complex cascade of events that occurs in response to tissue injury, infection, or inflammation, and involves the release of various cytokines and acute-phase proteins. TNF-α also induces a second wave of cytokines, including IL-6, IL-8, and C-reactive protein, which further amplify the inflammatory response and contribute to tissue damage and dysfunction. Interestingly, TNF-α is expressed not only by immune cells but also by microglia, astrocytes, and neurons in the central nervous system. Genetic polymorphisms associated with TNF up-regulation have been linked to increased susceptibility to Alzheimer's disease, suggesting that chronic low-grade inflammation mediated by TNF-α may contribute to the pathogenesis of this debilitating neurodegenerative disorder [27,28]. In a recent study, it was discovered that the combination of TNF-alpha and gamma-interferon has the ability to trigger the production of Aβ, a peptide notoriously linked to the development of Alzheimer's disease. Surprisingly, it was also found that Beta-amyloid, another protein involved in Alzheimer's pathogenesis, has the potential to activate microglial inflammatory pathways, which ultimately leads to neurotoxicity. This neurotoxicity is mediated by TNF-alpha, a cytokine produced by reactive microglia and monocytes, and is thought to contribute to the progressive neuronal loss seen in Alzheimer's disease. The discovery of the complex interplay between these proteins and cells provides a new avenue for potential therapeutic targets in the treatment of Alzheimer's disease [29].
The present study showed an increase in serum levels of TNF-α in AD vs the control group. This study is also in accordance with the results of Montgomery et al. [29], who reported that protein-related TNF-α inhibitors that modulate circulating TNF-α levels, such as etanercept and infliximab, have shown limited promise in altering the course of AD, because of their inability to efficiently traverse the blood-brain barrier [30]. In the study serum Fetuin-A levels were found significantly lower in AD patients compared to the control group. The results of previous studies [31,32] were parallel with our results. Fetuin-A is a cysteine protease inhibitor. Fetuin-A is an anti-inflammatory glycoprotein that declined during the systemic inflammatory process that is to say it is a negative acute phase reactant but remains controversial [33]. Among its biological effects, fetuin-A suppresses insulin sensitivity by inhibiting tyrosine kinase activity and auto-phosphorylation of insulin receptors [34]. As a result of these findings, it is suggested fetuin-A might play a role in the development of AD. Laughlin et al. [35], reported that anti-inflammatory attributes of Fetuin-A, it was also found to be neuroprotective and low Fetuin-A concentrations were associated with more severe cognitive decline in Alzheimer's disease patients. Recent studies have focused on the treatment of Alzheimer's disease using biological therapy, such as stem cells [36] or platelet-rich plasma [37], due to their anti-inflammatory effects leading to the suppression of inflammatory markers [38-40].

Conclusion.
High serum lipocalin-2, and TNF-α whereas low serum Fetuin-A levels in the AD patient group may suggest these factors have a role in AD pathogenesis.

Conflict of interest. No potential conflicts of interest are disclosed.

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