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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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SERUM LIPOCALIN-2, AND FETUIN-A LEVELS IN PATIENTS WITH ALZHEIMER'S DISEASE

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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, TNFa 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±5.0years 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 1. *Demographic characteristics of the studied groups.*

Parameter	**AD group (n=56)**	**Control group (n=56)**
Age (years)	79.4±5.0	78 .7±4.0
Gender (M/F)	20/36	25/31

Table 2. *Biochemical parameters of study groups.*

Parameters	**AD**	**Control**
Lipocalin-2 (ng/mL)	88.68 ± 32.1*	63 ± 28.5
TN-α	42.28±5.05*	35.19±5.07
Fetuin-A (ng/ml)	109.5 ± 10.8	128.4 ± 16.5*
*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-αinhibitors 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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REFERENCES

1. Sarhat ER. Evaluation of Melatonin and adipokines in patients with Alzheimer's disease. European Journal of Medicine. Series B. 2015;2:118-130.
2. Zorenko Y, Gubina-Vakulyck G, Pavlova O, et al. Dynamics of indicators of the endothelium morphofunctional state of the brain microcirculatory bed vessels in rats with nitrite-induced Alzheimer's type dementia on the background of mesenchymal stem cell administration. Medicinski Časopis. 2021;55.
3. Entedhar R. Sarhat. Altered serum marker of thyroid profile and antioxidant enzymes in individuals Alzheimer's disease. Int Res J Pharm. 2019;10:56-60.
4. Camargo CH, Justus FF, Retzlaff G, et al. The action of anti-TNF-α drugs on the progression of Alzheimer's disease: A case report. Dementia & Neuropsychologia. 2015;9:196-200.
5. Swardfager W, Lanctôt K, Rothenburg L, et al. A meta-analysis of cytokines in Alzheimer's disease. Biological psychiatry. 2010;68:930-941.
6. Hamad MS, Sarhat ER, Sarhat Th R, et al. Impact of Serum Adropin and Irisin in Iraqi patients with Congestive Heart Failure. P J M H S. 2021;15:497-499.
7. Sarhat ER. Study the levels of Leptin, and Adiponectin with Paraoxonase in Obese Individuals (male & female). Tikrit Journal of Pure Science. 2015;20:14-20.
8. Ahmed SE, Sarhat ER, Neda Awni, et al. Altered Serum Marker of Adipokines Profile in Breast Cancer Women. Indian Journal of Forensic Medicine & Toxicology. 2021;15:2598-2604.
9. Sarhat ER, Wadi SA, Mahmood AR, et al. Measurement of the Levels of Salivary Lipocalin-2 and C-reactive protein in Women with Polycystic Ovarian Syndrome. Tikrit Journal for Dental Sciences. 2019;7.
10. Elkhidir AE, Eltaher HB, Mohamed AO. Association of lipocalin-2 level, glycemic status and obesity in type 2 diabetes mellitus. BMC Research Notes. 2017;10:285.
11. Sedeeq BI, Sarhat ER, Wadee SA, et al. Desloratadine -Induced Histological and Biochemical changes in the kidneys of Rats. Teikyo Medical Journal. 2021;44:2970-2978.
12. Ze-Lin Sun, Qi-Ying Xie, Gong-Liang Guo, et al. "Serum Fetuin-A Levels in Patients with Cardiovascular Disease: A Meta-Analysis," BioMed Research International. 2014.
13. Sindhu S, Akhter N, Shenouda S, et al. Plasma fetuin-A/α2-HS-glycoprotein correlates negatively with inflammatory cytokines, chemokines, and activation biomarkers in individuals with type-2 diabetes. BMC Immunol. 2016;17:33.
14. Wang H, Li W, Zhu S, et al. Peripheral administration of fetuin-A attenuates early cerebral ischemic injury in rats. Journal of Cerebral Blood Flow & Metabolism. 2010;30:493-504.
15. Nangami GN, Watson K, Parker-Johnson K, et al. Fetuin-A (α2HS-glycoprotein) is a serum chemo-attractant that also promotes invasion of tumor cells through Matrigel. Biochemical and biophysical research communications. 2013;438:660-665.
16. Ip JP, Nocon AL, Hofer MJ, et al. Lipocalin 2 in the central nervous system host response to systemic lipopolysaccharide administration. Journal of neuroinflammation. 2011;8:1-6.
17. Hamdi AQ, Sarhat ER, Nagham Hasan Ali, et al. Evaluation of Lipocalin-2 and Visfatin, and Vitamin (D,C, and E) in Serum of Diabetic Patients with Chronic Periodontitis. Indian Journal of Forensic Medicine & Toxicology. 2021;15:1668-1674.
18. Mucha M, Skrzypiec AE, Schiavon E, et al. Lipocalin-2 controls neuronal excitability and anxiety by regulating dendritic spine formation and maturation. Proc Natl Acad Sci U S A. 2011;108:18436-18441.
19. Kang SS, Ren Y, Liu CC, et al. Lipocalin-2 protects the brain during inflammatory conditions. Molecular psychiatry. 2018;23:344-350.
20. Bi F, Huang C, Tong J, et al. Reactive astrocytes secrete lcn2 to promote neuron death. Proc Natl Acad SciU S A. 2013;110:4069-4074.
21. Jang E, Lee S, Kim JH, et al. Secreted protein lipocalin-2 promotes microglial M1 polarization. FASEB J. 2013;27:1176-1190.
22. Serot JM, Béné MC, Faure GC. Choroid plexus, aging of the brain, and Alzheimer's disease. Frontiers in Bioscience-Landmark. 2003;8:515-521.
23. Choi J, Lee HW, Suk K. Increased plasma levels of lipocalin 2 in mild cognitive impairment. J Neurol Sci. 2011;305:28-33.

24. Probert L. TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. Neuroscience. 2015;302:2-2.
25. Sarhat ER, Saeed HS. Effects of lycopene on paraoxonase and adipokines parameters in streptozotocin-induced diabetic rabbits. J Nat & Med Sci. 2017;18:1-8.
26. Yan J, Fu Q, Cheng L, et al. Inflammatory response in Parkinson's disease. Molecular medicine reports. 2014;10:2223-2233.
27. Sarhat ER, Wadi SA, Sedeeq BI, et al. Study of histopathological and biochemical effect of Punica granatum L. extract on streptozotocin-induced diabetes in rabbits. Iraqi Journal of Veterinary Sciences. 2019;33:189-194.
28. Tobinick E, Gross H, Weinberger A, et al. TNF-alpha Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study. Medscape General Medicine. 2006;8:25.
29. Montgomery SL, Mastrangelo MA, Habib D, et al. Ablation of TNF-RI/RII expression in Alzheimer's disease mice leads to an unexpected enhancement of pathology: implications for chronic pan-TNF-α suppressive therapeutic strategies in the brain. The American journal of pathology. 2011;179:2053-2070.
30. Albagoa ZR, Thanoon IA, Abdulla FI, et al. Etanercept in patients with ankylosing spondylitis: effectiveness and rate of response. MMSL. 2022;91:266-273.
31. Sattlecker M, Kiddle SJ, Newhouse S, et al. Alzheimer's disease biomarker discovery using SOMAscan multiplexed protein technology. Alzheimer's & Dementia. 2014;10:724-734.
32. Ix JH, Wassel CL, Kanaya AM, et al. Fetuin-A and incident diabetes mellitus in older persons. Jama. 2008;300:18A,-8.
33. Entedhar R. Sarhat, Siham A. Wadi, Neda Awni, et al. Evaluation of Vimentin and Some Biochemical Parameters in the Blood of Acute Myocardial Infarction Patients Egypt J Chem. 2022;65:221-226.
34. Smith ER, Nilforooshan R, Weaving G, et al. Plasma fetuin-A is associated with the severity of cognitive impairment in mild-tomoderate Alzheimer's disease. J Alzheimers Dis. 2011;24:327-333.
35. Laughlin GA, McEvoy LK, Barrett-Connor E, et al. Fetuin-A, a new vascular biomarker of cognitive decline in older adults. Clinical endocrinology. 2014;81:134-140.
36. Shin JY, Park HJ, Kim HN, et al. Mesenchymal stem cells enhance autophagy and increase β-amyloid clearance in Alzheimer disease models. Autophagy. 2014;10:32-44.
37. Shen YX, Fan ZH, Zhao JG, et al. The application of platelet-rich plasma may be a novel treatment for central nervous system diseases. Medical hypotheses. 2009;73:1038-1040.
38. Shephard MT, Merkhan MM, Forsyth NR. Human Mesenchymal Stem Cell Secretome Driven T Cell Immunomodulation Is IL-10 Dependent. International Journal of Molecular Sciences. 2022;23:13596.
39. Merkhan MM, Shephard MT, Forsyth NR. Physoxia alters human mesenchymal stem cell secretome. Journal of Tissue Engineering. 2021;12:20417314211056132.
40. Yousif HA, Alzamily AA, Alsalman IA. Anti-inflammatory activity of platelet-rich plasma treatment in the inflammation management of knee osteoarthritis: experimental study. MMSL. 2022.