Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Effect of regular exercise on ocular inflammation and mitochondrial biogenesis in experimental Alzheimer's disease model

Süleyman Okudan[1*], Tuğba Sezer[2], Emine Tınkır Kayıtmazbatır[1], Muaz Belviranlı[2], Nilsel Okudan[2]

[1]Selcuk University Faculty of Medicine, Department of Ophthalmology, 42130, Konya, Turkey
[2]Selcuk University Faculty of Medicine, Department of Physiology, 42130, Konya, Turkey

Article Info

Article history:

Received: January 02, 2025
Accepted: February 28, 2025
Published: March 31, 2025

Use your device to scan and read the article online

Abstract

This study investigates the effects of regular exercise on inflammation and mitochondrial biogenesis in the eye using a controlled experimental Alzheimer's disease (AD) model. Twenty-four male Wistar rats were divided into four groups: control, Alzheimer, exercise, and Alzheimer with exercise. Molecular markers, including Nuclear Factor Kappa B (NF-κB), Fibronectin Type III Domain-Containing Protein 5 (FNDC5), Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (PGC-1α), Sirtuin 1 (SIRT1) were analyzed through real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) Matrix Metalloproteinase 2 (MMP-2), and Interleukin-1 Beta (IL-1β) were analyzed enzyme-linked immunosorbent assay (ELISA) to evaluate exercise-induced changes in inflammation and mitochondrial function. NF-κB levels were significantly elevated in the Alzheimer group, reflecting neuroinflammation, while exercise partially mitigated these effects. Exercise increased FNDC5, PGC-1α, and SIRT1 levels, suggesting a role in promoting neuroprotection and mitochondrial biogenesis. However, MMP-2 and IL-1β effects were primarily observed at the gene expression level, without substantial changes in protein levels. The use of an Alzheimer-specific model reduced confounding factors, such as age-related pathologies, providing a clearer perspective on Alzheimer-associated ocular changes. These findings highlight the potential of exercise in modulating key molecular pathways involved in AD.

Keywords: Alzheimer's disease, Exercise, Mitochondrial biogenesis, Neuroinflammation, NF-κB, PGC-1α, SIRT1.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative condition that gradually impairs cognitive abilities and functional capacity [1]. It is the primary cause of dementia in middle-aged and elderly populations [2] The prevalence of AD rises with age, affecting less than 1% of individuals under 60 years old and more than 40% of those over 85 [3]. Studies have categorized risk factors for cognitive decline and dementia into two groups: modifiable factors, such as diet, physical activity, cognitive stimulation, hypertension, and obesity, and non-modifiable factors like age and genetics. Notably, up to 40% of dementia cases related to modifiable risk factors could be prevented [4]. Delaying the onset and progression of AD by one year or achieving a 10% reduction per decade in modifiable lifestyle risk factors could reduce the global burden of Alzheimer's dementia by approximately 9 million cases by 2050 [5].

Ophthalmological assessments have revealed various ocular changes in patients with central nervous system (CNS) disorders [6]. The eye, as an extension of the brain, shares a common embryological origin with it, making it a promising model for studying AD [7]. The neural and vascular similarities between the eye and brain encourage the identification of ocular biomarkers for AD [8]. Several ocular structures that exhibit pathological changes could serve as potential biomarkers, referred to as "oculomics," for detecting and monitoring AD [9]. Research has established a link between AD and glaucoma, suggesting both are age-related neurodegenerative conditions with shared pathophysiological mechanisms [10]. Additionally, increasing evidence indicates parallels between AD and age-related macular degeneration (AMD), including neuroinflammation, microvascular dysfunction, and metabolic and oxidative stress [11].

Multiple studies highlight the importance of consistent, long-term exercise and physical activity as modifiable interventions for managing various medical conditions [12]. Exercise positively impacts brain structure and function, particularly in aging populations, and benefits common ocular diseases, including dry eye disease (DED), cataracts, myopia, glaucoma, diabetic retinopathy (DR), and AMD [13]. However, the specific mechanisms underlying these effects, especially in humans, remain incompletely understood [14].

Neuroinflammation plays a pivotal role in AD progres-

* Corresponding author.
E-mail address: suleymanokudan@selcuk.edu.tr (S. Okudan).
Doi: http://dx.doi.org/10.14715/cmb/2025.71.3.14

sion. Nuclear Factor Kappa B (NF-κB), a key inflammatory transcription factor, promotes the expression of pro-inflammatory genes, exacerbating neuronal degeneration. Reactive astrocytes and microglial cells further contribute to inflammation by releasing cytokines that drive AD progression [15,16]. Proteins like Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α) and Sirtuin-1 (SIRT1) are crucial in modulating inflammation and reducing amyloid-beta plaques [17-19]. SIRT1 also helps regulate the metabolism of amyloid-beta and tau proteins, which are central to AD pathology, thereby slowing neurodegeneration [19]. Additionally, exercise-induced Fibronectin Type III Domain-Containing Protein 5 (FNDC5/irisin) offers neuroprotective benefits by mitigating brain inflammation [20]. Matrix metalloproteinases (MMPs) are linked to mechanisms that prevent amyloid plaque accumulation in both brain and ocular tissues [21].

Recognizing the critical role of inflammation regulation in AD progression, this study investigates the impact of regular exercise on inflammation and mitochondrial biogenesis in ocular tissues within an experimental Alzheimer's model. Specifically, biomarkers associated with neuroinflammation and cellular stress responses, including PGC-1α, FNDC5, SIRT1, and NF-κB, were analyzed. Additionally, levels of Matrix Metalloproteinase-2 (MMP-2) and Interleukin-1 beta (IL-1β), indicators of inflammation and tissue remodeling, were examined.

2. Materials and methods

2.1. Study approval and sample size determination

The study protocol was approved by the Experimental Animals Ethics Committee of Selcuk University Experimental Medicine Application and Research Center (Protocol number: 2024/66).

All experiments comply with ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Studies were carried out in accordance with Guidance on the operation of the Animals (Scientific Procedures) Act 1986 and associated guidelines, EU Directive 2010/63 for the protection of animals used for scientific purposes or the NIH (National Research Council) Guide for the Care and Use of Laboratory Animals (PDF) or those of an equivalent internationally recognized body.

In this study, sample size was determined using G-power software (version 3.1.9.2) with 80% power, 0.05 alpha level, and 0.25 effect size, focusing on $A\beta_{1-42}$ and tau protein levels, which are biological markers of AD. Power analysis determined that a minimum of 6 animals per group was required, a number consistent with that found in similar studies on experimental animals in the literature.

2.2 Experimental Alzheimer model and study design

The flow of the experiment is demonstrated in Fig 1.The study included 24 male Wistar rats aged 3-4 months, divided into four groups: control (n=6), Alzheimer (n=6), exercise (n=6), and Alzheimer plus exercise (n=6). The rats were housed in polycarbonate cages under a 12-hour light-dark cycle with controlled environmental conditions (temperature: 22 ± 2 °C, humidity: 50%). Food and water were provided *ad libitum*.

- Control Group (n=6): No treatment was administered; only physiological saline was given as a vehicle, and tissue samples were collected at the end of the study.

- Alzheimer Group (n=6): Administered daily doses of 60 mg/kg D-galactose intraperitoneally and 200 mg/kg $AlCl_3$ orally for 10 weeks, followed by tissue collection [22].

- Exercise Group (n=6): Subjected to a treadmill exercise protocol at 25 m/min for 45 minutes per day, 5 days per week for 10 weeks, and tissue samples were collected [23,24].

- Alzheimer plus Exercise Group (n=6): Administered daily doses of 60 mg/kg D-galactose intraperitoneally and 200 mg/kg AlC_{l3} orally and underwent the same exercise protocol as the exercise group for 10 weeks, followed by tissue collection.

The exercise protocol included a 1-week adaptation period as follows:
1st day: 10 m/min, 10 min
2nd day: 20 m/min, 10 min
3rd day: 25 m/min, 10 min
4th day: 25 m/min, 20 min
5th day: 25 m/min, 30 min

To mitigate treadmill stress, control group rats underwent mild exercise at 10 m/min for 5 minutes twice weekly. The effectiveness of this exercise protocol on the experimental Alzheimer's model has been shown in our previous studies [24]. After the 10-week intervention, all rats were euthanized by cervical dislocation, and eye tissues were harvested for analysis.

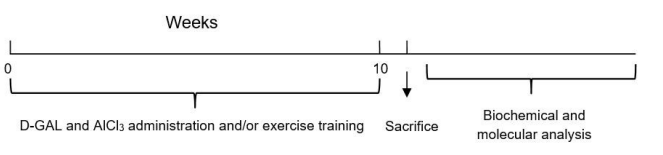

Fig. 1. Study design.

2.3. Biochemical and molecular analyses

2.3.1. Real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis

Measurement of gene expression was performed for SIRT, FNDC5, PGC-1α, and NF-κB using specific primers, and housekeeping gene GAPDH. Total RNAs were isolated from the eye tissue using the RiboZol RNA extraction reagent (Cat No: N580, VWR International, USA) and reverse transcribed into cDNA using iScript cDNA Synthesis Kit (Cat No: 1708891, Bio-Rad Laboratories, CA, USA). Real-time quantitative PCR was performed with SYBR Green qPCR Master Mix (Cat No: 1708880, iQ SYBR Green Supermix, Bio-Rad Laboratories, CA, USA) on a real-time PCR system (CFX-96, Bio-Rad Laboratories, CA, USA). The Ct values were used to calculate the relative expression by the $2^{-\Delta\Delta Ct}$ method [25], setting the control as 1.0. Primary designs used for analysis are shown in Table 1.

2.3.2. Enzyme-linked immunosorbent assay (ELISA) analyses

Eye tissue samples f were homogenized using ice-cold phosphate-buffered saline (pH: 7.4) To extract supernatants, the samples were centrifuged at 12,000 g for 10 min at 4 °C. Commercially available ELISA kits were used to determine the serum levels of IL-1β (Cat No: E2206Ra; BT LAB, Shanghai, China) and MMP2 (Cat No: E0315Ra; BT LAB, Shanghai, China). The intra-assay coefficient of variance (CV) was 4–6%, whereas the inter-assay CV was

Table 1. Forward and reverse primers of genes used for qRT-PCR experiments.

Gene	Primer sequence
NF-κB	Forward GGTTACGGGAGATGTGAAGATG Reverse: GTGGATGATGGCTAAGTGTAGG
SIRT1	Forward: TCCTGTGGGATACCTGACTT Reverse: AGGCGAGCATAAATACCATCTC
PGC-1α	Forward: CAGCAAGTCCTCCACTTACTAC Reverse: CAGCAAGTCCTCCACTTACTAC
FNDC5	Forward: GGGACAAGAACCTGGCTAAA Reverse: GGAAGCCAGGAGGGAAATAAA
GAPDH	Forward: ACTCCCATTCTTCCACCTTTG Reverse: CCCTGTTGCTGTAGCCATATT

5–7%. Every assay was conducted strictly in accordance with the manufacturer's instructions.

2.4. Statistical analysis

Data analysis was conducted using SPSS software version 25.0. All data are presented as mean ± standard deviation. Normality and homogeneity of variances were assessed, and two-way analysis of variance (ANOVA) was employed to evaluate the effects of Alzheimer's disease and exercise on the measured variables. Where significance was observed, Bonferroni-adjusted post hoc tests were performed. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. RT-PCR results

Figure 2 summarizes the PCR results for each group: Control (C), Alzheimer (A), Exercise (E), and Alzheimer with Exercise (A+E). NF-κB expression levels in group A were significantly higher than the groups C and E. In group A+E, NF-κB expression was significantly higher than in group E ($p<0.05$). SIRT1 expression was measured to be significantly higher in group E than in group A, C and A+E ($p<0.05$). PGC-1α expressions were also significantly higher in groups A, C and A+E ($p<0.05$). In group A PGC-1α expressions were significantly lower than group C and A+E. FNDC5 expressions were observed to be significantly higher in group AE compared to groups C and A ($p<0.05$). In group A, FNDC5 expression levels were significantly lower than in group E.

3.2 ELISA results

Figure 3 summarizes the ELISA results for each group. MMP2 levels were found to be significantly higher in group E compared to group A+E ($p<0.05$). There were no statistically significant differences between groups in terms of IL-1β levels.

4. Discussion

In this study, we examined the molecular markers NF-κB, FNDC5, PGC-1α, SIRT1, MMP-2, and IL-1β across four groups: Alzheimer's, exercise, control, and Alzheimer with exercise. The aim was to explore how exercise modulates these pathways in the context of AD. According to the findings obtained from this study, in the experimental AD model, inflammation increases, while mitochondrial biogenesis is impaired especially at the level of gene expression in the eye tissue. Ten weeks of exercise training can reverse this condition by partially alleviating inflammation and increasing mitochondrial biogenesis. Although previous studies have shown that mitochondrial biogenesis in the retina is impaired in AD [26], to our knowledge there is no study investigating the expression levels of FNDC5/irisin.

NF-κB levels were significantly elevated in the Alzheimer's group, reflecting heightened neuroinflammatory activity. This aligns with prior research identifying NF-κB as a key driver of inflammation in AD, where its activation in microglia and astrocytes perpetuates a cycle of pro-inflammatory cytokine release, neuronal damage, and Aβ plaque accumulation [16, 27]. While NF-κB levels were reduced in the Alzheimer with exercise group compared to the Alzheimer group, they remained higher than in the exercise-only group. This suggests that exercise partially mitigates inflammatory signaling but does not fully counteract the chronic neuroinflammation inherent to AD pathology. Exercise is known to suppress NF-κB activation and reduce inflammatory gene expression [28]; however, the persistent cellular stress and inflammation in AD likely sustain elevated NF-κB activity. In the These findings em-

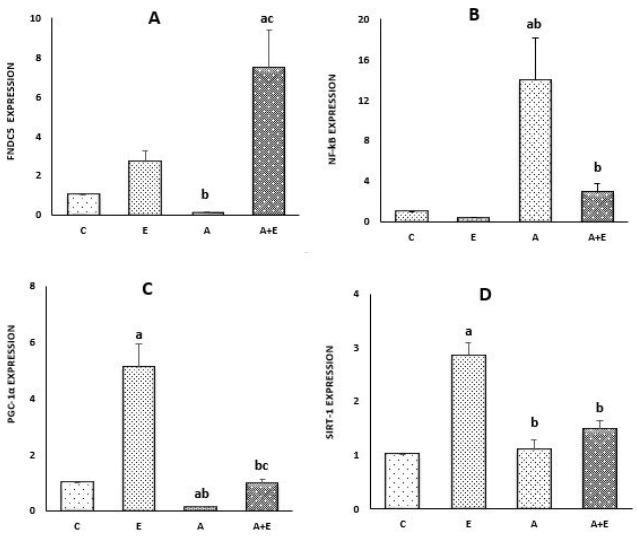

Fig. 2. Gene expression results of FNDC5 (A), NF-κB (B), PGC-1α (C) and SIRT-1 (D). "C" Control group, "E" Exercise group, "A" Alzheimer group, "A+C" Alzheimer with exercise group. A: $^{b}p<0.05$ compared with group E. acp<0.05 compared with group C and A. B: abp<0.05 compared with group C and E. $^{b}p<0.05$ compared with group E. C: a $p<0.05$ compared with group C. ab $p<0.05$ compared with group C and E. bcp<0.05 compared with group E and A. D: a $p<0.05$ compared with group C. $^{b}p<0.05$ compared with group E.

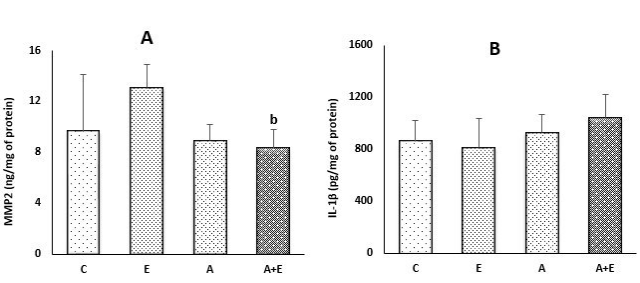

Fig. 3. ELISA results of MMP-2 (A) and IL-1β (B). "C" Control group, "E" Exercise group, "A" Alzheimer group, "A+C" Alzheimer with exercise group. A: $^{b}p<0.05$ compared with group E.

phasize the importance of directly targeting NF-κB as part of therapeutic strategies for AD.

Irisin, derived from FNDC5 and induced by exercise, plays a critical role in promoting cognitive health and neuroprotection. The Alzheimer group displayed lower irisin levels than the exercise group, consistent with evidence that neurodegenerative conditions reduce irisin levels and that physical activity can restore them [29]. Notably, the Alzheimer with exercise group had higher irisin levels than the exercise-only group, suggesting potential compensatory or adaptive responses to exercise in the presence of AD pathology. This may reflect enhanced sensitivity to exercise-induced irisin production under neurodegenerative conditions. The elevated irisin levels in the Alzheimer with exercise group, compared to both the control and Alzheimer groups, suggest that exercise stimulates irisin production even in pathological states. Irisin's known role in enhancing hippocampal neurogenesis, synaptic plasticity, and inflammation reduction underscores its therapeutic potential in addressing AD-related processes [30, 31]. Clinical studies have shown increased inflammation and impaired mitochondrial biogenesis and irisin levels in blood samples and post-mortem brain tissues from AD patients. Regular exercise reversed this by reducing inflammation and improving mitochondrial biogenesis in blood samples from AD patients [32-34].

PGC-1α levels were significantly higher in the exercise group than in the control group, consistent with its established role in enhancing mitochondrial biogenesis and oxidative stress resistance [35]. This coactivator is crucial for mitochondrial biogenesis and energy metabolism, enhancing resistance to oxidative stress, which is essential for maintaining neuronal health and plasticity [36, 37]. However, the Alzheimer group showed significantly lower PGC-1α levels compared to both the control and exercise groups, reflecting mitochondrial dysfunction commonly associated with AD. In the Alzheimer with exercise group, PGC-1α levels were partially restored compared to the Alzheimer group, although they remained lower than in the exercise-only group. This suggests that while exercise may counteract some mitochondrial impairments caused by AD, it cannot fully reverse them. Mechanisms involving amyloid precursor protein and presenilin in AD may suppress PGC-1α expression, exacerbating mitochondrial deficits [38].

Exercise significantly increased SIRT1 levels in the exercise group compared to both the control and Alzheimer groups, consistent with findings that physical activity upregulates SIRT1, a critical mediator of neuroprotection and inflammation regulation [39, 40]. Increased SIRT1 can enhance mitochondrial biogenesis, counteract oxidative stress, and mitigate neuroinflammation, all of which are critical for maintaining neuronal health [41]. SIRT1 levels were also higher in the Alzheimer with exercise group than in the Alzheimer group, indicating a partial recovery effect from exercise. However, this increase was not statistically significant, suggesting that AD pathology may suppress the full benefits of exercise-induced SIRT1 upregulation. Downregulation of SIRT1 in AD exacerbates neuroinflammation and mitochondrial dysfunction, impairing the brain's resistance to oxidative stress. SIRT1's role in modulating the NF-κB pathway underscores its importance in controlling AD-related inflammation [42].

MMP-2 levels were highest in the exercise group, followed by the control, Alzheimer, and Alzheimer with exercise groups. Exercise-induced mechanical stress and tissue remodeling likely explain the increase in MMP-2 levels in the exercise group [43]. The MMP pathway has been shown to be present in brain tissue with the potential to modulate the free levels of MMPs that can degrade β-amyloid [44]. In contrast, the lower MMP-2 levels in the Alzheimer group compared to the control suggest dysregulation or consumption due to chronic inflammation and excessive Aβ accumulation. While MMP-2 plays a protective role in degrading Aβ, its overactivation in AD may contribute to tissue damage and blood-brain barrier breakdown, leading to depletion. In the Alzheimer with exercise group, MMP-2 levels remained lower than in the exercise-only group, indicating that AD pathology may limit the exercise-induced increase in MMP-2. Additionally, the findings suggest that the observed effects may have remained at the gene expression level and were not fully reflected in protein measurements, possibly due to post-transcriptional regulation or protein turnover mechanisms. This dual role of MMP-2 as both a protective enzyme and a contributor to pathological processes highlights the complexity of its regulation in AD [21, 45].

IL-1β levels followed a gradient across groups, with the lowest levels in the exercise group, followed by the control, Alzheimer, and Alzheimer with exercise groups. However, these differences were not statistically significant, suggesting that IL-1β variations did not substantially affect inflammatory responses across the groups. IL-1β is a key pro-inflammatory cytokine involved in neuroinflammatory processes in AD [46]. Although elevated IL-1β levels are known to exacerbate neurodegenerative pathways, the lack of significant differences in this study indicates that AD pathology does not dramatically amplify IL-1β beyond control levels. Similar to MMP-2, it is possible that the effects of exercise and AD pathology on IL-1β were restricted to the gene expression level and did not translate into significant changes at the protein level. A larger sample size and the combined analysis of multiple cytokines are needed to gain a more comprehensive understanding of the inflammatory landscape in AD [47].

This study highlights the complex interplay between exercise and molecular markers of inflammation, mitochondrial function, and neuroprotection in Alzheimer's disease. While exercise provides partial benefits, the pathological mechanisms of AD may restrict these effects, particularly at the protein level, emphasizing the need for therapeutic strategies targeting both gene expression and protein translation to achieve more substantial outcomes. Alzheimer's disease and its ocular manifestations highlighted that certain risk factors, pathophysiological mechanisms, and age-related histopathological changes are common across various conditions. This makes it essential to carefully select subjects to minimize the potential influence of other diseases on the ocular findings. In our study, using a controlled experimental Alzheimer's model allowed us to focus specifically on Alzheimer's-related changes in the eye, reducing the likelihood that the observed findings are influenced by age-related or other pathological conditions. This approach may provide a clearer perspective on the ocular effects of Alzheimer's disease.

Possible limitations of this study based on the AD model should also be considered. While animal models provide valuable information about the pathophysiology

of AD, they may not fully reflect the complexity or clinical progression of the disease in humans. Ocular changes observed in experimental models may differ significantly from those in humans, limiting the generalizability of the findings. These limitations highlight the need for further research to confirm and extend the results and provide a more comprehensive understanding of AD and its ocular manifestations. Future studies should specifically examine the role of mitochondrial biogenesis in AD pathology in specific areas such as the retina and further elucidate possible changes not only at the gene expression level but also at the protein level.

In the experimental AD model, inflammation is increased, while mitochondrial biogenesis is impaired, particularly at the gene expression level in the eye tissue. Ten weeks of exercise training can reverse this situation by partially attenuating inflammation and increasing mitochondrial biogenesis. This study highlights the potential of regular exercise to reduce inflammation in the eye and enhance mitochondrial biogenesis in the eye, providing a promising non-pharmacological approach to manage AD-associated ocular changes.

Significance statement

This study highlights the potential of regular exercise to reduce inflammation and enhance mitochondrial biogenesis in the eye, offering a promising non-pharmacological approach for managing Alzheimer's disease-related ocular changes.

CRediT authorship contribution statement

Süleyman Okudan: Writing – original draft, Methodology, Investigation, Formal analysis.
Tuğba Sezer: Investigation, Formal analysis, Data curation, Visualization
Emine Tınkır Kayıtmazbatır: Methodology, Investigation, Conceptualization, Data curation
Muaz Belviranlı: Writing – review & editing, Formal analysis, Data curation, Conceptualization
Nilsel Okudan: Supervision, Validation, Methodology, Investigation

Disclosure statement

All the authors have found no conflict of interest to claim.

Data availability

All data are included in the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL (2015) Alzheimer's Disease. Nat Rev Dis Primers 1:15056. doi: 10.1038/nrdp.2015.56
2. Iqbal K, Grundke-Iqbal I (2010) Alzheimer's Disease, A Multifactorial Disorder Seeking Multitherapies. Alzheimers Dement. 6:420-424. doi: 10.1016/j.jalz.2010.04.006
3. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y (2014) Epidemiologic Studies of Modifiable Factors Associated With Cognition and Dementia: Systematic Review and Meta-Analysis. BMC Public Health 14:643. doi: 10.1186/1471-2458-14-643
4. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N (2020) Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission. Lancet. 396:413-446. doi: 10.1016/S0140-6736(20)30367-6
5. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for Primary Prevention of Alzheimer's disease: An Analysis of Population-Based Data. Lancet Neurol 13:788-794. doi: 10.1016/S1474-4422(14)70136-X
6. London A, Benhar I, Schwartz M (2013) The Retina as a Window to the Brain-from Eye Research to CNS Disorders. Nat Rev Neurol 9:44-53. doi: 10.1038/nrneurol.2012.227.
7. Romaus-Sanjurjo D, Regueiro U, López-López M, Vázquez-Vázquez L, Ouro A, Lema I, Sobrino T (2022) Alzheimer's Disease Seen through the Eye: Ocular Alterations and Neurodegeneration. Int J Mol Sci 23:2486. doi: 10.3390/ijms23052486
8. Singh AK, Verma S (2020) Use of Ocular Biomarkers as a Potential Tool For Early Diagnosis of Alzheimer's Disease. Indian J Ophthalmol 68:555-5561. doi: 10.4103/ijo.IJO_999_19
9. Majeed A, Marwick B, Yu H, Fadavi H, Tavakoli M (2021) Ophthalmic Biomarkers for Alzheimer's Disease: A Review. Front Aging Neurosci 13:720167. doi: 10.3389/fnagi.2021.720167
10. Mancino R, Martucci A, Cesareo M, Giannini C, Corasaniti MT, Bagetta G, Nucci C (2018) Glaucoma and Alzheimer Disease: One Age-Related Neurodegenerative Disease of the Brain. Curr Neuropharmacol 16:971-977. doi: 10.2174/1570159X16666171206144045
11. Frost S, Guymer R, Aung KZ, Macaulay SL, Sohrabi HR, Bourgeat P, Salvado O, Rowe CC, Ames D, Masters CL, Martins RN, Kanagasingam Y (2016) AIBL Research Group. Alzheimer's Disease and the Early Signs of Age-Related Macular Degeneration. Curr Alzheimer Res 13:1259-1266. doi: 10.2174/1567205013666160603003800
12. Pedersen BK, Saltin B (2015) Exercise as Medicine - Evidence for Prescribing Exercise as Therapy in 26 Different Chronic Diseases. Scand J Med Sci Sports Suppl 3:1-72. doi: 10.1111/sms.12581
13. Zhang Q, Jiang Y, Deng C, Wang J (2024) Effects and Potential Mechanisms of Exercise and Physical Activity on Eye Health and Ocular Diseases. Front Med (Lausanne) 11:1353624. doi: 10.3389/fmed.2024.1353624
14. Stillman CM, Esteban-Cornejo I, Brown B, Bender CM, Erickson KI (2020) Effects of Exercise on Brain and Cognition Across Age Groups and Health States. Trends Neurosci 43:533-543. doi: 10.1016/j.tins.2020.04.010
15. Medeiros R, LaFerla FM (2013) Astrocytes: Conductors of the Alzheimer Disease Neuroinflammatory Symphony. Exp Neurol 239:133-138. doi: 10.1016/j.expneurol.2012.10.007
16. Sun E, Motolani A, Campos L, Lu T (2022) The Pivotal Role of NF-kB in the Pathogenesis and Therapeutics of Alzheimer's Disease. Int J Mol Sci 23:8972. doi: 10.3390/ijms23168972
17. Qin W, Haroutunian V, Katsel P, Cardozo CP, Ho L, Buxbaum JD, Pasinetti GM (2009) PGC-1alpha Expression Decreases in the Alzheimer Disease Brain as a Function of Dementia. Arch Neurol 66:352-361. doi: 10.1001/archneurol.2008.588
18. Rosales MAB, Shu DY, Iacovelli J, Saint-Geniez M (2019) Loss of PGC-1α in RPE Induces Mesenchymal Transition and Promotes Retinal Degeneration. Life Sci Alliance 2:e201800212. doi: 10.26508/lsa.201800212
19. Mehramiz M, Porter T, O'Brien EK, Rainey-Smith SR, Laws

SM (2023) A Potential Role for Sirtuin-1 in Alzheimer's Disease: Reviewing the Biological and Environmental Evidence. J Alzheimers Dis Rep 7:823-843. doi: 10.3233/ADR-220088.

20. Wang M, Huang X, Shu J, Li H, Yang T, Li N, Yang P (2024) Irisin Alleviates Autoimmune Uveitis Through Promoting Retinal Microglial M1 to M2 Phenotypic Polarization Mediated by HIF-1α Pathway. Inflammation. 2024:Sep 29. doi: 10.1007/s10753-024-02149-5.
21. Hussain AA, Lee Y, Zhang JJ, Francis PT, Marshall J (2017) Disturbed Matrix Metalloproteinase Pathway in Both Age-Related Macular Degeneration and Alzheimer's Disease. J Neurodegener Dis 22017:4810232. doi: 10.1155/2017/4810232.
22. Chiroma SM, Mohd Moklas MA, Mat Taib CN, Baharuldin MTH, Amon Z (2018) d-galactose and aluminium chloride induced rat model with cognitive impairments. Biomed Pharmacother 103:1602-1608. doi: 10.1016/j.biopha.2018.04.152
23. Belviranlı M, Gökbel H, Okudan N, Başaralı K (2012) Effects of grape seed extract supplementation on exercise-induced oxidative stress in rats. Br J Nutr 108:249-56. doi: 10.1017/S0007114511005496
24. Belviranlı M, Okudan N (2009) Voluntary, involuntary and forced exercises almost equally reverse behavioral impairment by regulating hippocampal neurotrophic factors and oxidative stress in experimental Alzheimer's disease model. Behav Brain Res 364:245-255. doi: 10.1016/j.bbr.2019.02.030
25. Park J, Kim JT, Lee SJ, Kim JC (2020) The Anti-Inflammatory Effects of Angiogenin in an Endotoxin Induced Uveitis in Rats. Int J Mol Sci 21:413. doi: 10.3390/ijms21020413
26. Masuzzo A, Dinet V, Cavanagh C, Mascarelli F, Krantic S (2016) Amyloidosis in Retinal Neurodegenerative Diseases. Front Neuro 7:127. doi: 10.3389/fneur.2016.00127
27. Thawkar BS, Kaur G (2019) Inhibitors of NF-κB and P2X7/NLRP3/Caspase 1 Pathway in Microglia: Novel Therapeutic Opportunities in Neuroinflammation Induced Early-Stage Alzheimer's Disease. J Neuroimmunol 326:62-74. doi: 10.1016/j.jneuroim.2018.11.010
28. Liu HW, Chang SJ (2018) Moderate Exercise Suppresses NF-κB Signaling and Activates the SIRT1-AMPK-PGC1α Axis to Attenuate Muscle Loss in Diabetic *db/db* Mice. Front Physiol 9:636. doi: 10.3389/fphys.2018.00636
29. de Freitas GB, Lourenco MV, De Felice FG (2020) Protective actions of exercise-related FNDC5/Irisin in memory and Alzheimer's disease. J Neurochem 155:602-611. doi: 10.1111/jnc.15039
30. Waseem R, Shamsi A, Mohammad T, Hassan MI, Kazim SN, Chaudhary AA, Rudayni HA, Al-Zharani M, Ahmad F, Islam A (2022) FNDC5/Irisin: Physiology and Pathophysiology. Molecules 27:1118. doi: 10.3390/molecules27031118
31. Bellettini-Santos T, Batista-Silva H, Marcolongo-Pereira C, Quintela-Castro FCA, Barcelos RM, Chiepe KCMB, Rossoni JV Jr, Passamani-Ambrosio R, da Silva BS, Chiarelli-Neto O, Garcez ML (2023) Move Your Body toward Healthy Aging: Potential Neuroprotective Mechanisms of Irisin in Alzheimer's Disease. Int J Mol Sci 2023 24:12440. doi: 10.3390/ijms241512440.
32. Jensen CS, Bahl JM, Østergaard LB, Høgh P, Wermuth L, Heslegrave A, Zetterberg H, Heegaard NHH, Hasselbalch SG, Simonsen AH (2019) Exercise as a potential modulator of inflammation in patients with Alzheimer's disease measured in cerebrospinal fluid and plasma. Exp Gerontol 121:91-98. doi: 10.1016/j.exger.2019.04.003
33. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, Gonçalves RA, Clarke JR, Beckman D, Staniszewski A, Berman H, Guerra LA, Forny-Germano L, Meier S, Wilcock DM, de Souza JM, Alves-Leon S, Prado VF, Prado MAM, Abisambra JF, Tovar-Moll F, Mattos P, Arancio O, Ferreira ST, De Felice FG (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 25:165-175. doi: 10.1038/s41591-018-0275-4
34. Ornish D, Madison C, Kivipelto M, Kemp C, McCulloch CE, Galasko D, Artz J, Rentz D, Lin J, Norman K, Ornish A, Tranter S, DeLamarter N, Wingers N, Richling C, Kaddurah-Daouk R, Knight R, McDonald D, Patel L, Verdin E, E Tanzi R, Arnold SE (2024) Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. Alzheimers Res Ther 16:122. doi: 10.1186/s13195-024-01482-z
35. Bi X, Fang J, Jin X, Thirupathi A (2024) The Interplay Between BDNF and PGC-1 alpha in Maintaining Brain Health: Role of Exercise. Front Endocrinol (Lausanne). 15:1433750. doi: 10.3389/fendo.2024.1433750
36. Reutzel M, Grewal R, Joppe A, Eckert GP (2022) Age-Dependent Alterations of Cognition, Mitochondrial Function, and Beta-Amyloid Deposition in a Murine Model of Alzheimer's Disease-A Longitudinal Study. Front Aging Neurosci 14:875989. doi: 10.3389/fnagi.2022.875989
37. Robinson A, Grösgen S, Mett J, Zimmer VC, Haupenthal VJ, Hundsdörfer B, Stahlmann CP, Slobodskoy Y, Müller UC, Hartmann T, Stein R, Grimm MO (2014) Upregulation of PGC-1α Expression by Alzheimer's Disease-associated Pathway: Presenilin 1/Amyloid Precursor Protein (APP)/Intracellular Domain of APP. Aging Cell 13:263-272. doi: 10.1111/acel.12183
38. Aguirre-Rueda D, Guerra-Ojeda S, Aldasoro M, Iradi A, Obrador E, Ortega A, Mauricio MD, Vila JM, Valles SL (2015) Astrocytes Protect Neurons from Aβ1-42 Peptide-induced Neurotoxicity Increasing TFAM and PGC-1 and Decreasing PPAR-γ and SIRT-1. Int J Med Sci 12:48-56. doi: 10.7150/ijms.10035
39. Manjula R, Anuja K, Alcain FJ (2021) SIRT1 and SIRT2 Activity Control in Neurodegenerative Diseases. Front Pharmacol 11:585821. doi: 10.3389/fphar.2020.585821
40. Yang Y, Liu Y, Wang Y, Chao Y, Zhang J, Jia Y, Tie J, Hu D (2022) Regulation of SIRT1 and Its Roles in Inflammation. Front Immunol 13:831168. doi: 10.3389/fimmu.2022.831168
41. Zhang M, Tang Z (2023) Therapeutic Potential of Natural Molecules Against Alzheimer's Disease via SIRT1 Modulation. Biomed Pharmacother 161: 114474. doi: 10.1016/j.biopha.2023.114474
42. Watroba M, Szukiewicz D (2022) Sirtuins Promote Brain Homeostasis, Preventing Alzheimer's Disease Through Targeting Neuroinflammation. Front Physiol 13:962769. doi: 10.3389/fphys.2022.962769
43. Turkel I, Tahtalioglu S, Celik E, Yazgan B, Kubat GB, Ozerklig B, Kosar SN (2024) Time-course and Muscle-specific Gene Expression of Matrix Metalloproteinases and Inflammatory Cytokines in Response to Acute Treadmill Exercise in Rats. Mol Biol Rep 51:667. doi: 10.1007/s11033-024-09637-9
44. Ganguly K, Adhikary K, Acharjee A, Acharjee P, Trigun SK, Mutlaq AS, Ashique S, Yasmin S, Alshahrani AM, Ansari MY (2024) Biological Significance and Pathophysiological Role of Matrix Metalloproteinases in the Central Nervous System. Int J Biol Macromol 280):135967. doi: 10.1016/j.ijbiomac.2024.135967
45. Le NT, Xue M, Castelnoble LA, Jackson CJ (2007) The Dual Personalities of Matrix Metalloproteinases in İnflammation. Front Biosci 12:1475-87. doi: 10.2741/2161
46. Xie L, Lai Y, Lei F, Liu S, Liu R, Wang T (2015) Exploring the Association Between Interleukin-1β and Its Interacting Proteins in Alzheimer's Disease. Mol Med Rep 11:3219-3228. doi: 10.3892/mmr.2015.3183
47. Kumari S, Dhapola R, Sharma P, Singh SK, Reddy DH (2023) Implicative Role of Cytokines in Neuroinflammation Mediated AD and Associated Signaling Pathways: Current Progress in Mo-

lecular Signaling and Therapeutics. Ageing Res Rev 102098. doi: 10.1016/j.arr.2023.102098